Ethiopian Food and Drug Authority (EFDA)

Guideline for Registration of Medicines

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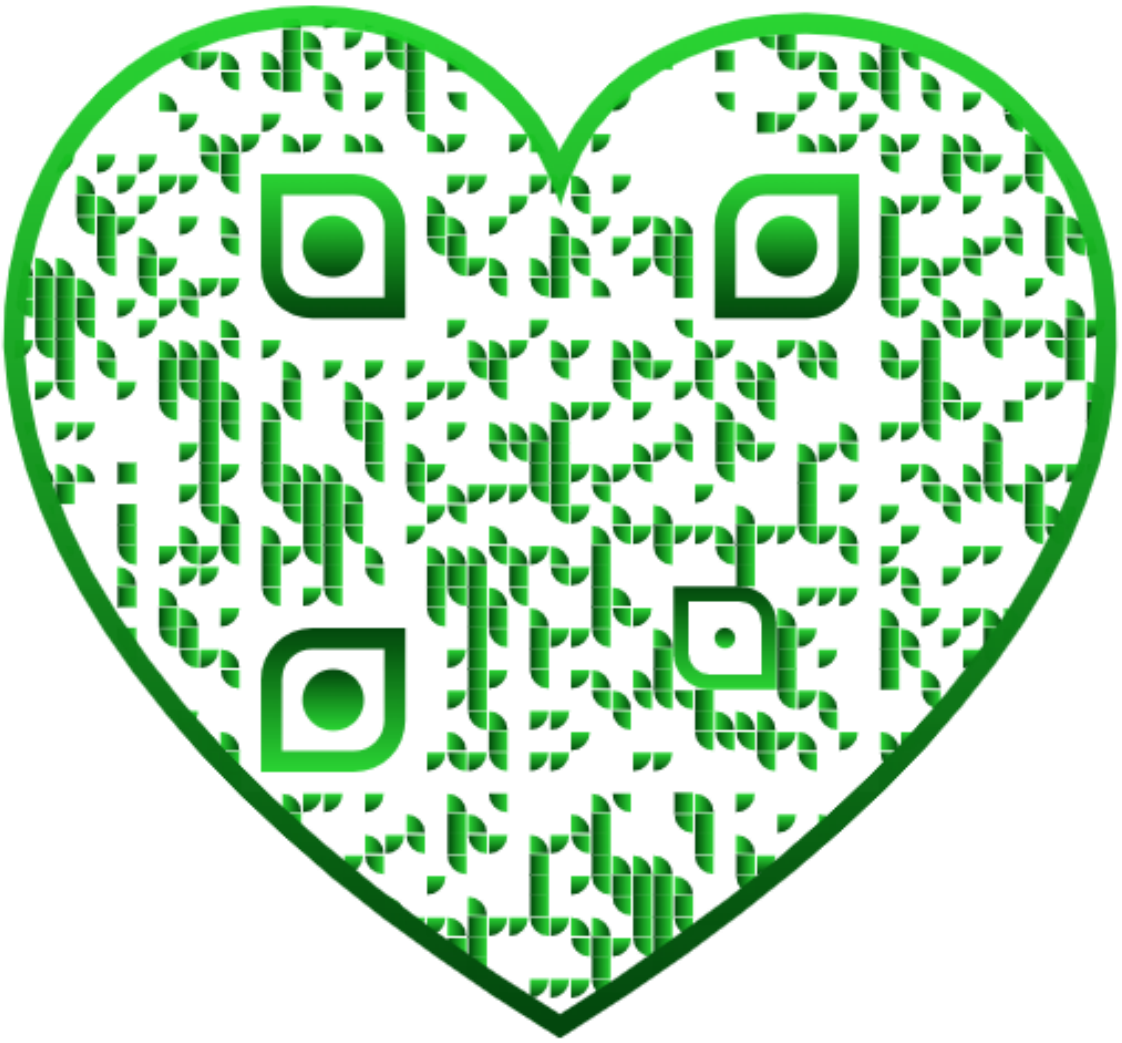

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ACRONYMS

API	Active Pharmaceutical Ingredient
APIMF	Active Pharmaceutical Ingredient Master File
BA	Bioavailability
BE	Bioequivalence
BCS	Biopharmaceutical Classification System
BMR	Batch Manufacturing Record
BPR	Batch Packaging Record
CEP	Certificate of Suitability
cGMP	Current Good Manufacturing Practices
CPP	Certificate of Pharmaceutical Product
CTD	Common Technical Document
DOS-PD	Dossier Overall Summary of Product Dossier
EFDA	Ethiopian Food and Drug Authority
EPAR	European Public Assessment Report
FDA	Food and Drug Administration
FDC	Fixed-dose Combination
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practices
ICH	International Council for Harmonisation
INN	International Non-proprietary Name
OOS	Out of Specification
OSD	Oral Solid Dosage
DP	Drug Product
PAR	Public Assessment Report
PD	Product Dossier
Ph. Eur.	European Pharmacopoeia
Ph. Int.	International Pharmacopoeia
PIL	Patient Information Leaflet
PQM	Promoting the Quality of Medicines Program
PV	Process Validation
PVC	Polyvinyl Chloride
QA	Quality Assurance
QC	Quality Control
RH	Relative Humidity
DS	Drug Substance
SMPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SRA	Stringent Regulatory Authority
UDAF	Unidirectional Air Flow
UDLAF	Unidirectional Laminar Air Flow
USAID	United States Agency for International Development
USP	U. S. Pharmacopeial Convention
WHO	World Health Organization

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INTRODUCTION

This Guideline succeeds the 2014 medicine registration Guideline, which was in use for medicine registration. It is prepared to inform manufacturers on what documentation should be submitted for registration of pharmaceutical products.

Guideline for Registration of Medicines in Ethiopia, 2014 was meant for registration of conventional medicines and biotech products. Considering the unique nature of the biotech products, the Authority has developed three different guidelines namely Guideline for Registration of Vaccine, Guideline for Registration of Biotherapeutic Protein Products Prepared by Recombinant DNA Technology and Guideline for Registration of Similar Biotherapeutic Product (SBPs). Furthermore, the current international guidelines, Expediting Medicine Market Authorization Strategy of the Authority, 2017 and development of an online electronic Regulatory Information System (eRIS) demanded for the revision of the existing medicine registration guideline.

This Guideline will serve as the conventional medicines registration and provide recommendations on the quality, safety and efficacy information for both active pharmaceutical ingredients (API) and finished pharmaceutical products (FPP) that should be submitted to the Authority.

The Guideline apply to Product dossiers (PDs) for products containing an API of synthetic or semi-synthetic; an API that has been previously authorized through a finished pharmaceutical product (FPP) by a stringent regulatory authority; and/or an API or its finished formulation officially included in a pharmacopoeia.

Applications for vaccine, Biotherapeutic Protein Products Prepared by Recombinant DNA Technology and Similar Biotherapeutic Products (SBPs) are covered by their respective registration guidelines of the Authority. In situations where this Guideline does not address the documentation requirement of a particular application, the matter shall be resolved on a case-by-case basis in consultation with the Authority.

Through the International Council for Harmonization (ICH) process, the Quality Module of the Common Technical Document (CTD) provides considerable harmonization of organization and format for registration documents. This recommended format in the M4Q, M4S, and M4E Guidelines for the quality, safety and efficacy information of registration applications have become widely accepted by regulatory authorities both within and beyond the ICH regions.

To facilitate the preparation of the PD, this Guideline is organized in accordance with the structure of the Common Technical Document-Quality (M4Q), Safety (M4S), and Efficacy (M4E) Guidelines developed by ICH and the WHO Guideline for submission of documents for multisource and innovator finished pharmaceutical products, TRS 986, Annex 6.

Once the application submitted to the Authority, different strategies will be followed during dossier assessment including abbreviated procedure for products approved by stringent regulatory authorities (Annex IV), risk based assessment, expedited assessment which includes conditional approval, collaborative approach for products prequalified by WHO; and

fast track designation of priority products such as HIV/AIDs, Malaria, TB, Vaccine, maternal, neonatal and child health (MNCH) products, anti-cancer drugs, vaccines, Hepatitis, New drug, drugs for "orphan diseases," drugs for emergent humanitarian aid and locally produced medicines. Applicants therefore are advised to consult expediting Medicine Market Authorization Strategy of the Authority, 2017 for proper categorization of the products and applying their application on the right track through the online eRIS of the Authority.

Applicants are advised to read and understand the contents of this Guideline and the instructions given under the "General Guidance and Format" before submitting a dossier to the Authority. Once a product is registered, its registration is valid for five years only. It is, therefore, mandatory for manufacturers to apply for re-registration by submitting the required information before the due date as described in Appendix 4 of this Guideline. Any variation to a registered medicine should be addressed as described in the "Guidelines for Submission of Post-Approval Variation Medicines Application, 2015."

All sections of the Guideline have been revised and extended based on the current international experience and a day-to-day work experiences with the previous guideline. The requirements set out in each section of the Guideline are general in nature, whereas applications must be considered and assessed on an individual basis; hence, such expressions as "when applicable," "where appropriate," and, "where relevant" have been frequently used in the Guideline.

Comments and suggestions are welcome and can be sent to the Ethiopian Food and Drug Authority, P.O. Box 5681, Addis Ababa, Ethiopia.

DEFINITIONS

The following definitions are provided to facilitate interpretation of the Guideline; they apply only to the words and phrases used in this Guideline. Although every effort has been made to use standard definitions, the words and phrases used here may have different meanings in other contexts and other documents.

Active pharmaceutical ingredient (API)
Any substance or combination of substances used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings. Drug Substance" and "Active Substance" are synonymous to "Active Ingredient."

API starting material
A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement or produced through in-house synthesis.

Applicant
The person or entity who submits a registration application of product to the Authority and responsible for the product information.

Authority
The Ethiopian Food and Drug Authority (EFDA)

Authorized local agent (Representative)
Any company or legal person established within a country or jurisdiction who has received a mandate from the manufacturer and/or license holder to act on his behalf for specified tasks with regard to the manufacturer's and/or license holder's obligations under legislation of the medicine and other regulatory guidance's issued by the Authority.

Batch records
All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

Bioavailability
The rate and relative amount of the administered drug which reaches the general circulation intact, or the rate and extent to which the API is absorbed from a drug product and becomes available at the site(s) of action.

Bioequivalence

Comparative bioavailability of two formulations of a drug. Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailability after administration in the same molar dose are similar to such a degree that their therapeutic effects can be expected to be essentially the same.

BCS (Biopharmaceutics Classification System) highly soluble
An API for which the highest dose included in the List of Essential Medicines for Ethiopia (if the API appear in the List of Essential Medicines) or, the highest dose strength available on the market as an oral solid dosage form is soluble in 250 ml or less of aqueous media over the pH range of 1.2–6.8 at 37ºC.

Clinical trial
Any systematic study on pharmaceutical products in human subjects whether in patients or non-patient volunteers in order to discover or verify the effects of, and/or identifies any adverse reaction to investigational products, and/or to study absorption, distribution, metabolism, and excretion of the products with the object of ascertaining their efficacy and safety.

Commitment batches
Production batches of an API or finished pharmaceutical product (FPP) for which the stability studies are initiated or completed post-approval through a commitment provided with the application.

Comparator product
A pharmaceutical product with which the generic product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety, and quality have been established.

Dosage Form
Formulation of an active ingredient(s) so that it can be administered to a patient in specified quantity/strength, e.g., tablets, capsules, injection solution, syrups, ointments, suppositories, etc. "Pharmaceutical Form" and "Finished Product" are synonymous to "Dosage Form."

Established multisource (generic) product
A multisource product that has been marketed by the applicant or manufacturer associated with the dossier for at least five years and for which at least 10 production batches were produced over the previous year, or, if less than 10 batches were produced in the previous year, not less than 25 batches were produced in the previous three years.

Excipient
Any component of a finished dosage forms other than the claimed therapeutic ingredient or active ingredients.

Finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labeling.

Formulation
The composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.

Immediate Container
That part of a product container which is in direct contact with the drug at all times.

Innovator pharmaceutical product
Generally, the pharmaceutical product that was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety, and quality.

Labeling
All labels and other written, printed, or graphic material that is affixed to a medicine or any of its container or wrapper and includes any legend, word, or mark attached to, inserted in, belonging to, or accompanying any medicine including: 1) the immediate container label; 2) cartons, wrappers, and similar items; 3) information materials, such as instructional brochures and package inserts.

Manufacturer
A company that carries out operations such as production, packaging, repackaging, labeling, and relabeling of products.

Marketing authorization
An official document issued for the purpose of marketing or free distribution of a product after evaluation of safety, efficacy, and quality of the product.

Marketing authorization holder
A manufacturer and/or a license holder of the product to whom marketing authorization certificate is issued (by the Authority) to sale or distribute the registered medicine in Ethiopian territory.

Master formula (MF)
A document or a set of documents specifying the starting materials, with their quantities and packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including in-process controls.

Multisource (generic) pharmaceutical products
Pharmaceutically equivalent or pharmaceutical alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

Officially recognized pharmacopoeia (or compendium)
Those pharmacopoeias recognized by the Authority, i.e., The International Pharmacopoeia (Ph.Int.), European Pharmacopoeia (Ph.Eur.), British Pharmacopoeia (BP), Japanese Pharmacopoeia (JP), and the United States Pharmacopeia (USP).

Ongoing stability study
The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm, and extend the projected re-test period (or shelf-life) of the API, or to confirm or extend the shelf-life of the FPP.

Pharmaceutical equivalents
Products are pharmaceutically equivalent if they contain the same amount of the same active ingredient(s) in the same dosage form, if they meet the same or comparable standards, and if they are intended to be administered by the same route.

Pilot-scale batch
A batch of an API or FPP manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch; for example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger; unless otherwise adequately justified.

Primary batch
A batch of an API or FPP used in a stability study from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf-life.

Production batch
A batch of an API or FPP manufactured at production scale by using production equipment in a production facility as specified in the registration dossier.

Specification
A document describing in detail the requirements with which the products or materials used or obtained during manufacture have to conform. Specifications serve as a basis for quality evaluation.

Stability
The ability of an active ingredient or a drug product to retain its properties within specified limits throughout its shelf-life. The chemical, physical, microbiological, and biopharmaceutical aspects of stability must be considered.

Starting materials for synthesis
Materials that mark the beginning of the manufacturing process as described in an application or in an APIMF. A starting material for a synthetic API is a chemical compound of defined molecular structure that contributes to the structure of the API.

Technical Person

A pharmacist authorized by the manufacturer and/or marketing authorization holder or authorized local agent to apply for the registration of medicines and corresponds with the Authority on related issues thereof.

Validation

The demonstration, with documentary evidence, that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

Variation

A change to any aspect of a pharmaceutical product including, but not limited to, a change to formulation, method, and site of manufacture or specifications for the finished product, ingredients, container and container labeling, and product information.

GENERAL GUIDANCE AND PRINCIPLE

The content of this Guideline should be read in conjunction with relevant information described in other existing World Health Organization (WHO) or International Council for Harmonization (ICH) reference documents and guidelines. The quality of existing active pharmaceutical ingredients (API) and corresponding multisource products should not be inferior to new APIs and innovator (comparator) finished pharmaceutical products (FPP). Therefore, the principles of the ICH Guidelines that are referenced throughout this document and other WHO guidelines may also equally apply to existing APIs and multisource products.

Scientific literature may be appropriate to fulfill the requirements for some of the information or parameters outlined in this Guideline (e.g., qualification of impurities). Furthermore, the requirements outlined in certain sections may not be applicable for the proposed API or FPP. In these situations, a summary and the full reference to the scientific literature should be provided, or the non-applicability of the requested information should be clearly indicated as such with an accompanying explanatory note.

Alternate approaches to the principles and practices described in this Guideline may be acceptable provided that they are supported by adequate scientific justification. It is also important to note that the Authority may request information or material, or define conditions not specifically described in this guidance, in order to adequately assess the safety, efficacy, and quality of the medicines prior to and after approval.

General format and guidance for preparation of dossiers

There may be a number of instances where repeated sections can be considered appropriate. Whenever a section is repeated, it should be made clear what the section refers to by creating a distinguishing heading, e.g., 3.2.S Drug substance (or API) (name, Manufacturer A).

The following are general recommendation for the submission of the dossier:

- For generic products in which a molecule of an FPP is registered in Ethiopia, Module 4 is not applicable;
- For generic FPP where bioequivalence is not required, Module 4 and Module 5 are not applicable; and,
- For generic products in which a molecule of an FPP and where a bioequivalence (BE) study is mandatory, Module 4 and Module 5 are not applicable except that the BE study report should be provided with the other modules of the dossier.

The following are recommendations for the presentation of the information in the *Quality Module* for different scenarios that may be encountered:

- The *Open part* (non-proprietary information) of each APIMF should always be included *in its entirety* in the product dossier (PD), as an annex to “3.2.S”;
- For an FPP containing more than one API—one complete “3.2.S” section should be provided for one API, *followed by* a complete “3.2.S” section for each additional API,

    - This may not be applicable for an API where a complete listing is not possible (e.g., multivitamin), applicant may choose the API(s) based on safety and criticality; however, when deemed necessary the Authority may request "3.2.S" for specific API;
- For an API from multiple manufacturers—one complete "3.2.S" section should be provided for the API from one manufacturer, *followed by* other complete "3.2.S" sections for an additional API manufacturer;
- For an FPP with multiple strengths (e.g., 5, 15, 200mg)—one complete "3.2.P" section should be provided with the information for the different strengths provided *within* the subsections;
- For an FPP with multiple container closure systems (e.g., bottles and unit dose blisters)—one complete "3.2.P" section should be provided with information for the different presentations provided *within* the subsections;
- For different dosage forms of FPPs (e.g., tablets and a parenteral product) —a separate dossier is required for each FPP;
- For an FPP supplied with reconstitution diluents (s)—one complete "3.2.P" section should be provided for the FPP, *followed by* the information on the diluents (s) in a separate part "3.2.P," as appropriate;
- For a co-blistered FPP, one complete "3.2.P" section should be provided for each product.

Well organized and carefully compiled documents will facilitate the evaluation process and decrease delays in the screening time. In contrast, poorly compiled documents may lead to an unnecessary waste of time for both the applicant and the Authority. Therefore, documents should have unambiguous contents: title, nature, and purpose should be clearly stated. They should be laid out in an orderly fashion. The content of the document should be easy to check (searchable) and copied.

Guidance for the applicant with regard to compilation and follow-up of the PD is listed here:

1. Paper selection: Paper size is A4. Margins for top, bottom, header, and footer are 12.5 mm, and left and right margins are 25mm.
2. Paragraph: Single line spacing.
3. Font: Times New Roman, letter space 0%, type size 12point.
4. The weight of the font should be in such a way that it text is legible when copied.
5. For registration of products, only web-based online submissions via eRIS at www.eris.efda.gov.et shall be accepted. To do this, the applicant shall assign a focal person and must be registered in the eRIS. To login into the online system, the applicant shall have a user name and password to access the online system. In addition, all files to be attached according to the CTD format shall be in pdf file format.
6. Applicant must ensure information on application and the online filled data are consistent.

7. The attached data and documents should be in the English language and/or English translation.
8. Any abbreviation should be clearly defined.
9. The compilation of the document should be outlined according to the respective modules and should be indexed or annotated as described in this Guideline in the Common Technical Document (CTD) format.
10. Evaluation and Notification: The application submitted for registration through eRIS will be evaluated chronologically according to the verification number generated by eRIS of the Authority, and the applicant will be notified of the results of its evaluation within 90 days of its submission to the Authority unless otherwise the workload not allow to do so.
11. Fast Track Registration: Antimalarial, antiretroviral, anti-tuberculosis medicines, maternal, neonatal and child health (MNCH) products, anti-cancer drugs, vaccines, Hepatitis, New drug, drugs for "orphan diseases" and drugs for emergent humanitarian aid shall have priority for evaluation and registration.
12. In case of requests to change the contents of application of the product, after reviewing of the screening application, the applicant needs to follow the variation guideline.
13. Supplement period: The applicant should respond to the requested query within six months of notification about further information requests such as the missing elements and/or clarification. If a supplemental submission is not executed within the specified period, urge to be supplemented within 15 days shall follow. If the supplement document is not submitted within the urge period or the contents of replenishment is inappropriate, the speculation shall be clarified, and the application shall be rejected. However, if the applicant calls for an extension, the submission period shall be determined based on the speculation.
14. Brand (Trade) name of medicines should not be identical and misleading. Generally, the first and last three letters of any trade name should not be identical with a registered product in Ethiopia.
15. The agent or the manufacturer and/or license holder of the product should appoint a technical person who is able to understand this (and related guidelines of the Authority), registration process of products, and who can communicate with the assessors in cases of need of clarification for the queries raised by the Authority that may either be product-related or administrative issues.

The CTD is organized into five *modules*; Module 1 is specific to the Authority which includes Administrative and Product information. Modules 2, 3, 4, and 5 are intended to be common for all situations.

The following Modular format of PDs in the CTD content should always be considered during dossier preparation for registration submission to the Authority:

Module 1 – Administrative and product information

1.1. Cover Letter
1.2. Table of Contents of the Application, including Module 1 (Modules 1-5)
1.3. Application Form
1.4. Agency Agreement
1.5. Good Manufacturing Practice Certificate and Certificate of Pharmaceutical Product
1.6. Certificate of Suitability (CEP), if any
1.7. Product Information
1.7.1. Summary of Product Characteristics
1.7.2. Labeling Information (immediate and outer label)
1.7.3. Patient Information Leaflet (PIL)
1.8. Evidence for an Application Fee
Module 2 – Dossier Overall Summary of Product Dossier (DOS-PD)
2.1 PD Table of Contents (Modules 2-5)
2.2 PD Introduction
2.3 Quality Overall Summary of Product Dossier (QOS-PD)
2.4 Nonclinical Overview – generally not applicable for multisource products (some exceptions may apply)
2.5 Clinical Overview
2.6 Nonclinical Written and Tabulated Summaries – generally not applicable for multisource products (some exceptions may apply)
2.7 Clinical Summary – generally not applicable for multisource products
Module 3 – Quality
3.1 Table of Contents of Module 3
3.2 Body of Data
3.3 Literature References
Module 4 – Nonclinical Study Reports – generally not applicable for multisource products (some exceptions may apply)
4.1 Table of Contents of Module 4
4.2 Study Reports
4.3 Literature References
Module 5 – Clinical Study Reports
5.1 Table of Contents of Module 5
5.2 Tabular Listing of all Clinical Studies
5.3 Clinical Study Reports
5.3.1 Reports of Biopharmaceutical Studies (mainly BE study reports for generic products)
5.3.2 Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials
5.3.3 Reports of Human Pharmacokinetic (PK) Studies
5.3.4 Reports of Human Pharmacodynamic(PhD) Studies
5.3.5 Reports of Efficacy and Safety Studies

5.3.6 Reports of Post-Marketing Experience
5.3.7 Case Report Forms and Individual Patient Listings – generally not applicable for multisource products (some exceptions may apply)
5.4 Literature References

MODULE 1: ADMINSTRATIVE AND PRODUCT INFORMATION

1.1. Covering Letter

Dated and signed letter for submission of the dossier by mentioning the product included in the dossier from the manufacturer and/or local agent responsible for registration.

1.2. Table Contents of Modules 1 to 5

Table of contents of Module 1 through Module 5 (of the PD) should be provided in Module 1.

1.3. Application Form

Complete application form on eRIS system using https://www.eris.efda.gov.et/login. The application form provided in Annex I may facilitate the filling of the application in the online platform.

1.4. Agency Agreement

i. All foreign medicine manufacturers who import or offer for import into the Ethiopian Market must identify local Agent or Local Representative to start the medicine registration process. The local Agent or Local Representative must be physically located in the Ethiopia and will serve as the primary and/or default point of contact between EFDA and the medicine manufacturers
ii. An agency agreement should be made between the manufacturer of the product for registration and the agent responsible for Medicine Registration, medicine import, distribution, and sale of the product in Ethiopia as per the template prescribed by the authority (Annex 6). Where the company manufactures the product at two or more places, the agreement and responsibility of each party made between the manufacturers should be submitted. In such a case, the agency agreement between the local agent and the manufacturer should be the site where the file is kept and the applicant for registration is registered.
iii. The agreement should be signed by both parties and such is what is to be presented. The seal/stamp of both parties should also be affixed to the document for agency agreement.
iv. The agreement should specify the local agent/representative to handle the medicine registration process. In case the manufacturer wishes to have more than one distributor, this has to be mentioned in the agreement; the appointed agent(s)/representative(s) are responsible for correspondence and complete compliance with regulatory requirements pertaining to the product distribution life cycle in the country.
v. The agreement should state that if any fraud or unsuspected and unacceptable adverse event occurs to the consumer under normal utilization, all the party's (local agents, manufacturer, and/or license holder) mentioned in the agreement will be responsible for collecting the product from the market and will be responsible for substantiating any related consequences.
vi. The agreement should specify that both parties are responsible for pharmacovigilance and post-marketing reporting of the product safety, quality, and

efficacy follow-up after marketing.

vii. Without a justifiable reason any commenced agency agreement shall not be terminated before one year.

viii. The agents representing Medicine manufacturer for Processing of medicine Registration should be a pharmacist in the pharmaceutical field, but not allowed to involve in the importation such Registered products without having valid competence certificate from EFDA and Trading License from Ethiopian Ministry of trade or equivalent institution designated by Ethiopian Government.

1.5. Responsibility of Local Agent or Local Representative

Act as liaisoning office and responsible for the following but not limited to

a. Reviewing and disseminating letters realised from EFDA regarding registered or product under registration to manufacturers and responding to all communications from EFDA including emergency communications;
b. Responding to questions concerning those drugs that are imported or offered for import to the Ethiopian Market;
c. Assisting EFDA in scheduling overseas cGMP inspections; and

1.6. Good Manufacturing Practice

i. A Copy of valid Good Manufacturing Practice (GMP) and Manufacturing License Certificate of FPP manufacturer should be provided.
ii. Inspection of the manufacturing site (by the Authority) may not be pre-request for submission of application for registration medicine. However, the manufacturing site should be inspected before issuance of the marketing authorization of the medicine under consideration. Thus, the copy of GMP certificate or GMP waiver letter issued by the Authority shall be requested prior to issuance of marketing authorization.

1.7. Certificate of Pharmaceutical Product

A valid Certificate of pharmaceutical product or marketing authorization certificate should be provided. Certificate of pharmaceutical product as a requirement for registration could be optional provided that valid cGMP Certificate and Market Authorization Certificate are submitted. The format of the CPP is provided in Annex II of this Guideline. The CPP should be valid. The CPP for the products should be in line with the explanatory notes of the CPP and summary of product characteristics as provided in Annex III of this Guideline.

1.8. Certificate of Suitability (CEP), if applicable

A complete copy of the Certificate of Suitability (CEP), including any annexes, should be provided in *Module 1.* The declaration of access for the CEP should be duly filled out by the CEP holder on behalf of the FPP manufacturer or applicant to the Authority.

In addition, a written commitment should be included that states the applicant will inform the Authority in the event that the CEP is withdrawn. It should also be acknowledged by the applicant that withdrawal of the CEP will require additional consideration of the API data requirements to support the PD. The written commitment should accompany the copy

of the CEP in Module 1(refer 3.2.S option 2 of this guideline for the detail of information require).

1.9. Product information

Product information including package insert, labeling, and summary of product characteristics (SmPC) should be provided in Module 1 of the dossier. All product information label statements are required to be in English and/or Amharic. Any information appearing in the product information (labels, PIL, and SmPC) should be based on scientific justification.

1.9.1. Summary of Product Characteristics

Recommended format for the content of the SmPC is provided in Annex III of this Guideline. The applicant is required to provide.

1.9.2. Labeling (immediate and outer label)

Only original labels or computer-ready color-printed labels are accepted for final approval. In the case where the text of the labels is printed directly on plastic bottles through a silk screen process, colored copies of these labels will be accepted for approval.

The titles for batch number, manufacturing, and expiry dates should be part of the printing (type written materials, stickers, etc., are not acceptable). If the labeling technology of the manufacturer is such that this information is to be printed on the label during production, a written commitment to show all the required information on the label of the finished product must be submitted. The contents of the label should at least contain:

a) The name of the product– brand and generic/International Non-proprietary Name (INN);
b) Pharmaceutical form and route of administration;
c) Qualitative and quantitative composition of active ingredient(s) and Special excipients such as lactose, Aspartame, preservative(s), and antioxidant (s);
d) The volume of the contents, and/or the number of doses, or quantity in container;
e) Directions to consult the package insert or the carton label for complete directions for use;
f) Handling and storage conditions;
g) License number of the manufacturer;
h) Batch number;
i) Manufacturing date;
j) Expiry date; and,
k) Name and address of manufacturer.

When the immediate container label is too small (in size) to contain all the above information, the label needs to contain at least information as indicated on a, b, c, d, f, h, i and j. Additionally, the label needs to contain logo of the manufacturer and/or license holder.

1.9.3. Patient Information Leaflet (PIL) or Package Insert

The general content of the PIL should be prepared in line with the content of the SmPC.

The information on leaflet of medicine that is included in the national essential medicine list of Ethiopia or widely circulated in Ethiopian market is required to be at least in English and Amharic. The PIL should not be described or presented in a manner that is false, misleading, or deceptive or is likely to create an erroneous impression regarding its use in any respect, either pictorially or in words.

1.10. Evidence for an application fee

Each application should be accompanied by a relevant service fee for registration. Applicants are advised to consult the current Rate of Service Fees Regulation of the Authority for the amount to be paid for application and contact the Authority for details of mode of payment.

MODULE 2: DOSSIER OVERALL SUMMARY (DOS)

The Dossier Overall Summary (DOS) is a summary that follows the scope and the outline of the body of data provided in Module 3, Module 4 and Module 5. The DOS should not include information, data, or justification that was not already included in Module 3, Module 4, and Module 5 or in other parts of the dossier.

The DOS should include sufficient information from each section to provide the assessors with an overview of the PD. The DOS should also emphasize critical key parameters of the product and provide, for instance, justification in cases where guidelines were not followed. The DOS should include a discussion of key issues that integrates information from sections in the Safety, Efficacy, and Quality Module and supporting information from other modules (e.g., qualification of impurities via toxicological studies), including cross-referencing to volume and page number in other Modules.

The Dossier Overall Summary–Product Dossiers (DOS-PD) template should always be completed and accompanied by the product dossier for registration with the Authority.

All sections and fields in the DOS-PD template, as indicated in Appendix 5, that would be applicable should be completed. It is understood that certain sections and fields may not apply and should be indicated as such by reporting “not applicable” in the appropriate area with an accompanying explanatory note. This DOS should not normally exceed 50pages, excluding tables and figures.

The use of tables to summarize the information is encouraged, where possible. The tables included in the DOS template may need to be expanded or duplicated as necessary (e.g., for multiple strengths), but should not be deleted or ignored without a reasonable explanatory note. These tables are included as illustrative examples of how to summarize information. Other approaches to summarize the information can be used if they fulfill the same purpose.

MODULE 3: QUALITY

3.1. Table of Contents of Module 3

A Table of Contents for the filed application should be provided.

3.2. Body of Data

3.2.S Drug Substance 1 (Name, Manufacturer)

The Authority, may accept API information in one or more of the following four options:

- Option 1: Confirmation of API prequalification document;
- Option 2: Certificate of suitability of the European Pharmacopoeia (CEP); or
- Option 3: API master file (APIMF) procedure; or
- Option 4: Full details in the PD.

The applicant should clearly indicate at the beginning of the API section (in the PD and in the QOS-PD) how the information on the API for each API manufacturer is being submitted. The API information submitted by the applicant/FPP manufacturer should include the following for each of the options used.

Option 1: Confirmation of API prequalification document

API prequalification is a procedure for manufacturers of APIs that are of interest to WHO. The procedure verifies both the quality of the API and that the API is manufactured in compliance with good manufacturing practices (GMP) (ICH Q7). Complementary information regarding a prequalified API is provided on the Prequalification of Medicines website and in the Confirmation of Prequalification document (CPQ).

A complete copy of the Confirmation of API Prequalification document should be provided in Module 1, together with the duly filled out authorization box in the name of the FPP manufacturer or applicant.

The applicant should supply the following information in the dossier, with data summarized in the QOS-PD.

- 3.2.S.1.3 General properties – discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the API manufacturer’s specifications, e.g. solubilities and polymorphs according to the guidance in this section.
- 3.2.S.2 If the sterility of the FPP is based upon the sterile manufacture of the API then data on the sterilization process together with full validation data should be provided.
- 3.2.S.3.1 Elucidation of structure and other characteristics – studies to identify polymorphs and particle size distribution, where applicable, according to the guidance in this section.
- 3.2.S.4.1 Specification – the specifications of the FPP manufacturer including all tests and limits of the API manufacturer's specifications and any additional tests and

acceptance criteria that are not controlled by the API manufacturer's specifications, such as polymorphs and/or particle size distribution.

- 3.2.S.4.2/3.2.S.4.3 Analytical procedures and validation – for any methods used by the FPP manufacturer in addition to those in the API manufacturer's specifications.
- 3.2.S.4.4 Batch analysis – results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.
- 3.2.S.5 Reference standards or materials – information on the FPP manufacturer's reference standards.
- 3.2.S.7 Stability – data to support the retest period if either the proposed retest period is longer or the proposed storage conditions are at a lower temperature or humidity than that of the prequalified API.

Option 2: Certificate of Suitability of the European Pharmacopoeia (CEP)

A complete copy of the CEP (including any annexes) should be provided in Module 1. The declaration of access for the CEP should be duly filled out by the CEP holder on behalf of the FPP manufacturer or applicant to the NMRA who refers to the CEP.

In addition, a written commitment should be included that the applicant will inform the NMRA in the event that the CEP is withdrawn. It should also be acknowledged by the applicant that withdrawal of the CEP would require additional consideration of the API data requirements to support the PD. The written commitment should accompany the copy of the CEP in Module 1.

Together with the CEP, the applicant should supply the following information in the dossier, with data summarized in the QOS-PD.

- 3.2.S.1.3 General properties – discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the CEP and European Pharmacopoeia (Ph. Eur.) monograph, e.g. solubilities and polymorphs according to the guidance in this section.
- 3.2.S.3.1 Elucidation of structure and other characteristics – studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable, according to the guidance in this section.
- 3.2.S.4.1 Specification – the specifications of the FPP manufacturer including all tests and limits of the CEP and Ph.Eur. monograph and any additional tests and acceptance criteria that are not controlled in the CEP and Ph.Eur. monograph, such as polymorphs and/or particle size distribution.
- 3.2.S.4.2/3.2.S.4.3 Analytical procedures and validation – for any methods used by the FPP manufacturer in addition to those in the CEP and Ph.Eur. monograph.
- 3.2.S.4.4 Batch analysis – results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.
- 3.2.S.5 Reference standards or materials – information on the FPP manufacturer's reference standards.

- 3.2.S.6 Container-closure system – specifications including descriptions and identification of primary packaging components. Exception: where the CEP specifies a container-closure system and the applicant declares the intention to use the same container closure system.
- 3.2.S.7 Stability– exception: where the CEP specifies a retest period that is the same as or of longer duration, and storage conditions which are at the same or a higher temperature and humidity as proposed by the applicant.

In the case of sterile APIs, data on the process for sterilization of the API, including validation data, should be included in the PD.

Option 3: API master file (APIMF) procedure

Full details of the chemistry, manufacturing process, quality controls during manufacturing and process validation for the API may be submitted to the Authority as an APIMF by the API manufacturer, for example, as outlined in the WHO Guidelines on active pharmaceutical ingredient master file procedure.

In such cases, the Open part (non-proprietary information) needs to be included in its entirety in the PD as an annex to 3.2.S. In addition, the applicant/FPP manufacturer should complete the following sections in the PD and QOS -PD in full according to the guidance provided unless otherwise indicated in the respective sections:

General information S.1.1–S.1.3

Manufacture S.2

Manufacturer(s) S.2.1

Description of manufacturing process and process controls S.2.2

Controls of critical steps and intermediates S.2.4

Elucidation of structure and other characteristics S.3.1

Impurities S.3.2

Control of the API S.4.1–S.4.5

Reference standards or materials S.5

Container-closure system S.6

Stability S.7.1– S.7.3

It is the responsibility of the applicant to ensure that the complete APIMF (i.e. both the applicant’s Open part and the API manufacturer's restricted part) is supplied to the Authority directly by the API manufacturer and that the applicant has access to the relevant information in the APIMF concerning the current manufacture of the API.

A copy of the letter of access should be provided in the PD Module 1. APIMF holders can use the guidance provided for the option "Full details in the PD" for preparation of the relevant sections of the Open and Restricted parts of their APIMFs. Reference can also be made to the APIMF guidelines.

The Authority will have a list of approved API with their license holder and manufacturing site. Applicant declaration need to mention that the API is similar to those API listed in the approved API list.

Option 4: Full details in the PD

Information on the 3.2.S Active pharmaceutical ingredient sections, including full details of chemistry, manufacturing process, quality controls during manufacturing and process validation for the API, should be submitted in the PD as outlined in the subsequent sections of these guidelines. The QOS-PD should be completed according to section 3.1 of these guidelines.

3.2.S.1 General Information (Name, Manufacturer)

3.2.S.1.1 Nomenclature (name, manufacturer)

Information on the nomenclature of the drug substance should be provided. For example:

- Recommended International Non-proprietary Name (INN);
- Compendial name, if relevant;
- Chemical name(s);
- Company or laboratory code;
- Other non-proprietary name(s) (e.g., national name, United States Adopted Name(USAN), Japanese Accepted Name (JAN), British Approved Name (BAN)) and Chemical Abstracts Service (CAS) registry number.
- The listed chemical names should be consistent with those appearing in scientific literature and those appearing on the product labeling information (e.g., summary of product characteristics; package leaflet, also known as patient information leaflet or PIL; or labeling). Where several names exist, the preferred name should be indicated.

3.2.S.1.2 Structure (name, manufacturer)

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

This information should be consistent with that provided in Section 3.2.S.1.1. For APIs existing as salts, the molecular mass of the free base or acid should also be provided.

3.2.S.1.3 General properties (name, manufacturer)

A list should be provided of physicochemical and other relevant properties of the drug substance. (Reference: ICH Guidelines Q6A and Q6B)

This information can be used in developing the specifications, in formulating FPPs, and in testing for release and stability purposes. The physical and chemical properties of the API

should be discussed, including the physical description, solubility in common solvents (e.g., water, alcohols, dichloromethane, acetone), quantitative aqueous pH solubility profile (e.g., pH 1.2 to 6.8, dose/solubility volume), polymorphism, pH and pKa values, UV absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygrocopicity, partition coefficient, etc. (See table in the DOS-PD). This list is not intended to be exhaustive but provides an indication as to the type of information that could be included.
Some of the more relevant properties to be considered for APIs are discussed below in greater detail.

Physical description
The description should include appearance, colour and physical state. Solid forms should be identified as being crystalline or amorphous (see 3.2.S.3.1 for further information on API solid forms).

Solubilities /quantitative aqueous pH solubility profile
The following should be provided whichever option is adopted for the submission of API data.

- The solubilities in a number of common solvents (e.g. water, alcohols, dichloromethane, and acetone).
- The solubilities over the physiological pH range (pH 1.2 to 6.8) in several buffered media in mg/ml. If this information is not readily available (e.g. in literature references), it should be generated in -house.
- For solid oral dosage forms, the dose/solubility volume as determined by:

$$Dose/solubilty\ volume = \frac{Largest\ dosage\ strength(mg)}{the\ minimum\ concentration\ of\ the\ API\left(\frac{mg}{ml}\right)*}$$

* corresponding to the lowest solubility determined over the physiological pH range (pH 1.2 to 6.8) and temperature (37 ± 0.5 °C).

In line with the Biopharmaceutics Classification System (BCS), highly soluble (or highly water soluble) APIs are those with a dose/solubility volume of less than or equal to 250 ml.

For example, compound A has as its lowest solubility at 37 ± 0.5 °C, 1.0 mg/ml at pH 6.8 and is available in 100 mg, 200 mg and 400 mg strengths. This API would not be considered a BCS highly soluble API as its dose/solubility volume is greater than 250 ml (400 mg/1.0 mg/ml = 400 ml).

Polymorphism

As recommended in ICH's CTD-Q Questions and answers/location issues document, the following refers to where specific data should be located in the PD:

- the polymorphic form(s) present in the proposed API should be listed in section 3.2.S.1.3;

- the description of manufacturing process and process controls (3.2.S.2.2) should indicate which polymorphic form is manufactured, where relevant;
- the literature references or studies performed to identify the potential polymorphic forms of the API, including the study results, should be provided in section 3.2.S.3.1;
- if a polymorphic form is to be defined or limited (e.g. for APIs that are not BCS highly soluble and/or where polymorphism has been identified as an issue), details should be included in 3.2.S.4.1–3.2.S.4.5.

Additional information is included in the sections mentioned in the above bullet points of these guidelines. In addition, 3.2.P.2.2.3 discusses considerations for control of the polymorphic form of the API in the FPP.

Particle size distribution

As recommended in ICH's CTD-Q Questions and answers/location issues document, the studies performed to identify the particle size distribution of the API should be provided in section 3.2.S.3.1 (refer to this section of these guidelines for additional information).

Information from literature

Supportive data and results from specific studies or published literature can be included within or attached to this section.

Reference documents: ICH Q6A.

3.2. S.2 Manufacture (Name, Manufacturer)

3.2. S.2.1 Manufacturer(s) (name, manufacturer)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

The facilities involved in the manufacturing, packaging, labelling, testing and storage of the API should be listed. If certain companies are responsible only for specific steps (e.g. milling of the API), this should be clearly indicated. This includes any manufacturing sites responsible for the preparation and supply of intermediates to the API manufacturer.

The list of manufacturers/companies should specify the actual addresses of production or manufacturing site(s) involved (including block(s) and units(s)), rather than the administrative offices. Telephone number(s), fax number(s) and e-mail address(es) should be provided.

A valid manufacturing authorization and certificate of GMP compliance should be provided for the production of APIs in the PD in Module 1. For manufacturers of API intermediates, the basis for establishing that these sites are operating under GMP should be provided.

3.2.S.2.2 Description of manufacturing process and process controls (name, manufacturer)

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls.

For a synthetic drug substance, a flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of

starting materials, intermediates, reagents and API reflecting stereochemistry, and identifies operating conditions and solvents.

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts, and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment, and operating conditions (e.g., temperature, pressure, pH, and time).

Alternate processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or filed in 3.2.S.2.5.

Where possible, and for confidentiality reasons, the holder of the APIMF can submit the restricted part of the APIMF to the Authority. In this case, if detailed information is presented in the restricted part, the information to be provided for this section of the applicant FPP PD includes a flow chart (including molecular structures and all reagents and solvents) and a brief outline of the manufacturing process, with special emphasis on the final steps, including purification procedures. However, for sterile APIs, full validation data on the sterilization process should be provided in the Open part (in cases where there is no further sterilization of the final product).

The following requirements apply in cases where the fourth option for submission of API information has been chosen, where full details are provided in the dossier.

As discussed in ICH Q7 and WHO Technical Report Series, No. 957, Annex 2, the point at which the API starting material is introduced into the manufacturing process is the starting point of the application of GMP requirements. The API starting material itself needs to be proposed and its choice justified by the manufacturer and accepted as such by assessors. The API starting material should be proposed, taking into account the complexity of the molecule, the proximity of the API starting material to the final API, the availability of the API starting material as a commercial chemical and the quality controls placed upon the API starting material. In the case where the precursor to the API is obtained by fermentation, or is of plant or animal origin, such a molecule can be considered the API starting material regardless of complexity.

A one-step synthesis may be accepted in exceptional cases, for example, where the API starting material is covered by a CEP, or where the API starting material is an API accepted through the APIMF procedure, or when the structure of the API is so simple that a one-step synthesis can be justified, e.g. ethambutol.

In addition to the detailed description of the manufacturing process according to ICH M4Q, the recovery of materials, if any, should be described in detail with the step in which they are introduced into the process. Recovery operations should be adequately controlled such that impurity levels do not increase over time. For recovery of solvents, any processing to improve the quality of the recovered solvent should be described.

Regarding recycling of filtrates (mother liquors) to obtain second crops, information should be available on maximum holding times of mother liquors and maximum number of times the material can be recycled. Data on impurity levels should be provided to justify recycling of filtrates.

Where there are multiple manufacturing sites for one API manufacturer, a comprehensive list in tabular form should be provided comparing the processes at each site and highlighting any differences; this includes preparation of the API intermediates from external suppliers. The manufacturing details described in this section should either be declared to be identical for all intermediate manufacturers involved in the preparation of the API, or each alternative manufacturing process employed should be described in this section, for each intermediate manufacturer, using the same level of detail as that supplied for the primary manufacturing process.

All solvents used in the manufacture (including purification and/or crystallization step(s)) should be clearly identified. Solvents used in the final steps should be of high purity. Use of recovered solvent in the final step or purification is not recommended unless the specification of the recovered solvent is essentially the same as the fresh solvent. It is essential that the quality standard applied to recovered solvents and the use of such solvents is validated thoroughly.

Where polymorphic/amorphous forms have been identified the form resulting from the synthesis should be stated. Where particle size is considered a critical attribute (see 3.2.S.3.1 for details), the particle size reduction method(s) (milling, micronization) should be described.

Justification should be provided for alternative manufacturing processes. Alternative processes should be explained using the same level of detail as is used to describe the primary process. It should be demonstrated that batches obtained by the alternative processes have the same impurity profile as the principal process. If the impurity profile obtained is different it should be demonstrated to be acceptable according to the requirements described under S.3.2.

It is acceptable to provide information on pilot-scale manufacture, provided it is representative of production scale and scale-up is reported immediately to the NMRA according to the requirements of the associated variation guidelines (e.g. WHO Technical Report Series, No. 981, 2013, Annex 3. (Reference documents: ICH Q7, Q11)

3.2. S.2.3 Control of materials (name, manufacturer)

Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials meet standards appropriate for their intended use should be provided, as appropriate (details in 3.2.A.2).

Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF is considered sufficient for this section.
The following requirements apply to the fourth option for submission of API information, where full details are provided in the dossier.

The API starting material should be fully characterized and suitable specifications proposed and justified, including, at a minimum, control for identity, assay, impurity content and any other critical attribute of the material. For each API starting material, the name and manufacturing site address of the manufacturer(s) should be indicated, including of those manufacturers supplying API starting material to an external intermediate manufacturer. A brief description of the preparation of the API starting material should be provided for each manufacturer, including the solvents, catalysts and reagents used. A single set of specifications should be proposed for the starting material that applies to material from all sources. Any future changes to the API starting material manufacturers, mode of preparation or specifications should be notified.

In general, the starting material described in the PD should:

- be a synthetic precursor of one or more synthesis steps prior to the final API intermediate. Acids, bases, salts, esters and similar derivatives of the API, as well as the racemate of a single enantiomer API, are not considered final intermediates;
- be a well-characterized, isolated and purified substance with its structure fully elucidated including its stereochemistry (when applicable);
- have well-defined specifications that include, among others, one or more specific identity tests and tests and limits for assay and specified, unspecified and total impurities;
- be incorporated as a significant structural fragment into the structure of the API.

Copies of the specifications for the materials used in the synthesis, extraction, isolation and purification steps should be provided in the PD, including starting materials, reagents, solvents, catalysts and recovered materials. Confirmation should be provided that the specifications apply to materials used at each manufacturing site. A certificate of analysis of the starting material should be provided. A summary of the information on starting materials should be provided in the QOS-PD.

The carry-over of impurities of the starting materials for synthesis into the final API should be considered and discussed.

A letter of attestation should be provided confirming that the API and the starting materials and reagents used to manufacture the API are *without* risk of transmitting agents of animal spongiform encephalopathies. When available, a CEP demonstrating Transmissible Spongiform Encephalopathy (TSE)-compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module 1.

3.2. S.2.4 Controls of critical steps and intermediates (name, manufacturer)

Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled should be provided.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided. Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF is considered sufficient for this section of the PD, with the exception of information that is also relevant for the applicant (see APIMF guidelines in WHO Technical Report Series, No. 948, Annex 4).

The following requirements apply to the fourth option for submission of API information, where full details are provided in the dossier.
The critical steps should be identified. These can be among others: steps where significant impurities are removed or introduced, steps introducing an essential molecular structural element such as a chiral entre or resulting in a major chemical transformation, steps having an impact on solid-state properties and homogeneity of the API that may be relevant for use in solid dosage forms.

Specifications for isolated intermediates should be provided and should include tests and acceptance criteria for identity, purity and assay, where applicable.
Where API intermediates are sourced externally, these materials should be controlled to a single specification maintained by the API manufacturer. Evidence of the quality of the supplied materials should be provided in the form of certificates of analysis for batches of intermediate, issued by the intermediate supplier and by the API manufacturer upon retesting.
(Reference: ICH Guideline Q6A)

3.2. S.2.5 Process validation and/or evaluation (name, manufacturer)

It is expected that the manufacturing processes for all APIs are properly controlled. If the API is prepared as sterile, a complete description should be provided for aseptic processing and/or sterilization methods. The controls used to maintain the sterility of the API during storage and transportation should also be provided.

Where the APIMF procedure is used, a cross-reference to the restricted part of the APIMF is considered sufficient for this section of the PD.
The following requirements apply to the fourth option for submission of API information, where full details are provided in the dossier.

The manufacturing processes for all APIs are expected to be properly controlled. If the API is prepared as sterile, a complete description should be provided of the aseptic processing and/or sterilization methods. The controls used to maintain the sterility of the API during storage and transportation should also be provided. Alternative processes should be justified and described (see guidance in 3.2.S.2.2 for the level of detail expected).

3.2.S.2.6 Manufacturing process development (name, manufacturer)

A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the API used in producing comparative

bioavailability or bio-waiver, scale-up, pilot, clinical and, if available, production scale batches.

Reference should be made to the API data provided in Section 3.2.S.4.4.
Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF is considered sufficient for this section of the PD.

The significance of the change should be assessed by evaluating its potential to impact the quality of the drug substance (and/or intermediate, if appropriate). For manufacturing changes that are considered significant, data from comparative analytical testing on relevant drug substance batches should be provided to determine the impact on quality of the drug substance. A discussion of the data, including a justification for selection of the tests and assessment of results, should be included.

Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) can also include nonclinical and clinical studies. Cross-reference to the location of these studies in other modules of the submission should be included.

3.2.S.3 Characterization (Name, Manufacturer)

3.2.S.3.1 Elucidation of structure and other characteristics (name, manufacturer)

Confirmation of structure based on, e.g., synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should also be included.

Elucidation of structure

The PD should include quality assurance (QA)-certified copies of the spectra, peak assignments, and a detailed interpretation of the data of the studies performed to elucidate and/or confirm the structure of the API. The DOS-PD should include a list of the studies performed and a conclusion from the studies that the results support the proposed structure.

For APIs that are not described in an officially recognized pharmacopoeia, the studies carried out to elucidate and/or confirm the chemical structure normally include elemental analysis, infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR), and mass spectra (MS) studies. Other tests could include X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC), for example, where polymorphism is identified as an issue.

For APIs that are described in an officially recognized pharmacopoeia, it is generally sufficient to provide copies of the IR spectrum of the API from each of the proposed manufacturer(s) runs concomitantly with a pharmacopoeial reference standard. See Section 3.2.S.5 for details on acceptable reference standards or materials.

Isomerism/stereochemistry

When an API is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the clinical or the comparative bio-studies, and information should be given as to the stereoisomer of the API that is to be used in the FPP.

Where the potential for stereoisomerism exists, a discussion should be included of the possible isomers that can result from the manufacturing process and the steps where chirality was introduced. The identicality of the isomeric composition of the API to that of the API in the comparator product should be established. Information on the physical and chemical properties of the isomeric mixture or single enantiomer should be provided, as appropriate. The API specification should include a test to ensure isomeric identity and purity.

The potential for inter-conversion of the isomers in the isomeric mixture, or racemisation of the single enantiomer should be discussed.

When a single enantiomer of the API is claimed for non-pharmacopoeial APIs, unequivocal proof of absolute configuration of asymmetric centers should be provided, such as determined by X-ray of a single crystal. If, based on the structure of the API, there is no potential for stereoisomerism, it is sufficient to include a statement to that effect.

Polymorphism

Many APIs can exist in different physical forms in the solid state. Polymorphism is characterized as the ability of an API to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice. Solvates are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent. If the incorporated solvent is water, the solvates are also commonly known as hydrates.

Polymorphic forms of the same chemical compound differ in internal solid-state structure and, therefore, may possess different chemical and physical properties, including packing, thermodynamic, spectroscopic, kinetic, interfacial, and mechanical properties. These properties can have a direct impact on API process-ability, pharmaceutical product manufacturability, and product quality/performance, including stability, dissolution and bioavailability. Unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences.

Applicants and API manufacturers are expected to have adequate knowledge about the polymorphism of the APIs used and/or produced. Information on polymorphism can come from the scientific literature, patents, compendia or other references to determine if polymorphism is a concern, e.g. for APIs that are not BCS highly soluble. In the absence of published data for APIs that are not BSC highly soluble, polymorphic screening will be necessary to determine if the API can exist in more than one crystalline form. Polymorphic screening is generally accomplished via crystallization studies using different solvents and conditions.

There are a number of methods that can be used to characterize the polymorphic forms of an API. Demonstration of a nonequivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism. XRPD can also be used to provide unequivocal proof of polymorphism. Other methods, including microscopy, thermal analysis (e.g., DSC, thermal gravimetric analysis and hot-stage microscopy) and spectroscopy (e.g., IR, Raman, solid-state nuclear magnetic resonance [ssNMR]) are helpful to further characterize polymorphic forms. Where polymorphism is a concern, the applicants/manufacturers of APIs should demonstrate that a suitable method, capable of distinguishing different polymorphs, is available to them.

Decision tree 4(1) of ICH Q6A can be used where screening is necessary, and 4(2) can be used to investigate if different polymorphic forms have different properties that may affect performance, bioavailability, and stability of the FPP, and to decide whether a preferred polymorph should be monitored at release and on storage of the API. Where there is a preferred polymorph, acceptance criteria should be incorporated into the API specification to ensure polymorphic equivalence of the commercial material and that of the API batches used in the comparative bioavailability or biowaiver studies. The polymorphic characterization of the API batches used in clinical, comparative bioavailability, or biowaiver studies by the above-mentioned methods should be provided. The method used to control polymorphic form should be demonstrated to be specific for the preferred form.
Polymorphism can also include solvation or hydration products (also known as pseudopolymorphs). If the API is used in a solvated form, the following information should be provided:

- specifications for the solvent-free API in 3.2.S.2.4, if that compound is a synthetic precursor;
- specifications for the solvated API including appropriate limits on the weight ratio of API to solvent (with data to support the proposed limits);
- a description of the method used to prepare the solvate in 3.2.S.2.2.

Particle size distribution

For APIs that are not BCS highly soluble contained in solid FPPs, or liquid FPPs containing un-dissolved API, the particle size distribution of the material can have an effect on the in vitro and/or in vivo behavior of the FPP. Particle size distribution can also be important in dosage form performance (e.g., delivery of inhalation products), achieving uniformity of content in low-dose tablets (e.g., 2 mg or less), desired smoothness in ophthalmic preparations, and stability of suspensions.

If particle size distribution is an important parameter, e.g., as in the above cases, results from an investigation of several batches of the API should be provided, including characterization of the batch(es) used in clinical and in the comparative bioavailability or biowaiver studies. API specifications should include controls on the particle size distribution to ensure consistency with the material in the batch(es) used in the comparative bioavailability and biowaiver studies (e.g., limits for d10, d50, and d90). The

criteria should be established statistically, based on the standard deviation of the test results from the previously mentioned studies.

The following are provided for illustrative purposes as possible acceptance criteria for particle size distribution limits:

- d10 not more than (NMT) 10% of total volume less than X µm
- d50 XX µm – XXX µm
- d90 not less than (NLT) 90% of total volume less than XXXX µm.

Other controls on particle size distribution can be considered acceptable, if scientifically justified.

Reference documents: ICH Q6A

3.2.S.3.2 Impurities (name, manufacturer)

Details on the principles for the control of impurities (e.g. reporting, identification and qualification) are outlined in the ICH Q3A, Q3B and Q3C impurity guidelines. Additional information to provide further guidance on some of the elements discussed in the ICH guidelines is outlined below.

Regardless of whether a pharmacopoeial standard is claimed, a discussion should be provided of the potential and actual impurities arising from the synthesis, manufacture, or degradation of the API. This should cover starting materials, by-products, intermediates, chiral impurities, and degradation products and should include the chemical names, structures, and origins. The discussion of pharmacopoeial APIs should not be limited to the impurities specified in the API monograph.

The tables in the DOS-PD template should be used to summarize the information on the API-related and process-related impurities. In the DOS-PD, the term *origin* refers to how and where the impurity was introduced (e.g., "Synthetic intermediate from Step 4 of the synthesis," "Potential by-product due to rearrangement from Step 6 of the synthesis"). It should also be indicated if the impurity is a metabolite of the API.

The ICH thresholds for reporting, identification (used to set the limit for individual unknown impurities) and qualification are determined on the basis of potential exposure to the impurity, e.g. by the maximum daily dose (MDD) of the API. For APIs available in multiple dosage forms and strengths having different MDD values, it is imperative that the thresholds and corresponding controls for each of the presentations be considered to ensure that the risks posed by impurities have been addressed. This is normally achieved by using the highest potential daily MDD, rather than the maintenance dose. For parenteral products the maximum hourly dose of the API should also be included.

It is acknowledged that APIs of semi-synthetic origin do not fall within the scope of the ICH impurity guidelines. However, depending on the nature of the API and the extent of the chemical modification steps, the principles for the control of impurities (e.g. reporting, identification and qualification) could also be extended to APIs of semi-synthetic origin. As an illustrative example, an API whose precursor molecule was derived from a fermentation process or a natural product of plant or animal origin that has subsequently

undergone several chemical modification reactions would generally fall within this scope, whereas an API whose sole chemical step was the formation of a salt from a fermentation product generally would not. It is understood that there is some latitude for these types of APIs.

Identification threshold

It is recognized by the pharmacopoeias that APIs can be obtained from various sources and thus can contain impurities not considered during the development of the monograph. Furthermore, a change in the production or source may give rise to additional impurities that are not adequately controlled by the official compendial monograph. As a result, each PD is assessed independently to consider the potential impurities that may arise from the proposed route(s) of synthesis. For these reasons, the ICH limits for unspecified impurities (e.g., NMT 0.10% or 1.0 mg per day intake (whichever is lower) for APIs having a maximum daily dose of ≤2 g/day) are generally recommended, rather than the general limits for unspecified impurities that may appear in the official compendial monograph that could potentially be higher than the applicable ICH limit.

Qualification of impurities

The ICH impurity guidelines should be consulted for options on the qualification of impurities. The limit specified for an identified impurity in an *officially recognized pharmacopoeia* is generally considered to be qualified. The following is an additional option for qualification of impurities in existing APIs:

The limit for an impurity present in an existing API can be accepted by comparing the impurity results found in the existing API with those observed in an innovator product using the same validated, stability-indicating analytical procedure (e.g., comparative high-performance liquid chromatography (HPLC) studies). If samples of the innovator product are not available, the impurity profile may also be compared to a different comparator (market leading) FPP with the same route of administration and similar characteristics (e.g., tablet versus capsule). It is recommended that the studies be conducted on comparable samples (e.g., samples of the same age) to obtain a meaningful comparison of the impurity profiles.

Levels of impurities generated from studies under accelerated or stressed storage conditions of the innovator or comparator FPP are not considered acceptable/qualified.

A specified impurity present in the existing API is considered qualified if the amount of the impurity in the existing API reflects the levels observed in the innovator or comparator (market leading) FPP.

Basis for setting the acceptance criteria

The basis for setting the acceptance criteria for the impurities should be provided. This is established by considering the identification and qualification thresholds for API-related impurities (e.g. starting materials, by-products, intermediates, chiral impurities or

degradation products) and the concentration limits for process-related impurities (e.g. residual solvents) according to the applicable ICH guidelines (e.g. Q3A (16), Q3C.
The qualified level should be considered as the maximum allowable limit. However, limits which are considerably wider than the actual manufacturing process capability are generally discouraged. For this reason, the acceptance criteria are also set taking into consideration the actual levels of impurities found in several batches of the API from each manufacturer, including the levels found in the batches used for the comparative bioavailability or biowaiver studies. When reporting the results of quantitative tests, the actual numerical results should be provided rather than vague statements such as "within limits" or "conforms". In cases where a large number of batches have been tested it is acceptable to summarize the results of the total number of batches tested with a range of analytical results.
If there are identified impurities specified in an official compendial monograph that are not controlled by the proposed routine in-house analytical procedure, a justification for their exclusion from routine analyses should be provided (e.g. "Impurities D, E and F listed in The International Pharmacopoeia (Ph.Int.) monograph are not potential impurities from the proposed route of synthesis used by manufacturer X"). If acceptable justification cannot be provided it should be demonstrated that the routine in-house method is capable of separating and detecting the impurities specified in the official compendial monograph at an acceptable level (e.g. 0.10%). If such a demonstration cannot be performed, a one-time study should be conducted applying the pharmacopoeial method to several recent batches to demonstrate the absence of impurities listed in the pharmacopoeial monograph.

ICH class II solvent(s) used prior to the last step of the manufacturing process may be exempted from routine control in API specifications if suitable justification is provided. Submission of results demonstrating less than 10% of the ICH Q3C limit (option I) of the solvent(s) in three consecutive production-scale batches or six consecutive pilot-scale batches of the API or a suitable intermediate would be considered acceptable justification. The last-step solvents used in the process should always be routinely controlled in the final API. The limit for residues of triethylamine (TEA) is either 320 ppm on the basis of ICH Q3C (option 1) or 3.2 mg/day on the basis of permitted daily exposure (PDE).

The absence of known, established, highly toxic impurities (genotoxic) used in the process or formed as a by-product should be discussed and suitable limits should be proposed. The limits should be justified by appropriate reference to available guidance's (e.g., EMEA/CHMP/QWP/251344/2006 or USFDA Guidance for Industry: Genotoxic and carcinogenic impurities in drug substances and products, recommended approaches, December 2008) or by providing experimental safety data or published data in peer-reviewed journals.

Residues of metal catalysts used in the manufacturing process and determined to be present in batches of API are to be controlled in specifications. This requirement does not apply to metals that are deliberate components of the pharmaceutical substance (such as a

counter ion of a salt) or metals that are used as a pharmaceutical excipient in the FPP (e.g., an iron oxide pigment). The guideline on the specification limits for residues of metal catalysts or metal reagents, EMEA/CHMP/SWP/4446/2000, or any equivalent approaches can be used to address this issue. The requirement normally does not apply to extraneous metal contaminants that are more appropriately addressed by GMP, WHO Good Distribution Practices for Pharmaceutical Products (GDP), or any other relevant quality provision such as the heavy metal test in monographs of recognized pharmacopoeias that cover metal contamination originating from manufacturing equipment and the environment.

(Reference documents: ICH Q3A, Q3C, Q6A)

3.2.S.4 Control of Drug Substance (name, manufacturer)

3.2.S.4.1 Specification (name, manufacturer)

The specification for the drug substance should be provided. Copies of the API specifications dated and signed by authorized personnel (e.g., the person in charge of the quality control or quality assurance department) should be provided in the PD, including specifications from each API manufacturer as well as those of the FPP manufacturer.

The FPP manufacturer's API specification should be summarized according to the table in the DOS-PD template under the headings tests, acceptance criteria, and analytical procedures (including types, sources, and versions for the methods).

- The s*tandard* declared by the applicant could be an officially recognized compendial standard (e.g.,Ph.Int.,Ph.Eur., BP, USP, JP) or a House (manufacturer's) standard.
- The *specification reference number and version* (e.g., revision number and/or date) should be provided for version control purposes.
- For the analytical procedures, the *type* should indicate the kind of analytical procedure used (e.g., visual, IR, UV, HPLC, laser diffraction); the *source* refers to the origin of the analytical procedure (e.g., Ph.Int.,Ph.Eur., BP, USP, JP, in-house); and the *version* (e.g., code number/version/date) should be provided for version control purposes.

In cases where there is more than one API manufacturer, the FPP manufacturer's API specifications should be one single compiled set of specifications that is identical for each manufacturer. It is acceptable to lay down in the specification more than one acceptance criterion and/or analytical method for a single parameter with the statement "for API from manufacturer A" (e.g., in the case of residual solvents).

Any non-routine testing should be clearly identified as such and justified along with the proposal on the frequency of non-routine testing.

The ICH Q6A guideline outlines recommendations for a number of *universal* and *specific tests* and criteria for APIs. [Reference: ICH Guidelines Q3A, Q3C, Q6A; officially recognized pharmacopoeia]

3.2.S.4.2 Analytical procedures (name, manufacturer)

The analytical procedures used for testing the drug substance should be provided. Copies of the in-house analytical procedures used to generate testing results provided in the PD, as well as those proposed for routine testing of the API by the FPP manufacturer should be provided. Unless modified, it is not necessary to provide copies of officially recognized compendial analytical procedures.

Tables for summarizing a number of the different analytical procedures and validation information (e.g., HPLC assay/impurity methods, gas chromatography (GC) methods) can be found in the 2.3.R Regional information section of the DOS-PD (i.e.,*2.3.R.2).* These tables should be used to summarize the in-house analytical procedures *of the FPP manufacturer* for determination of the residual solvents, assay, and purity of the API, in section 2.3.S.4.3 of the DOS-PD. Other methods used to generate assay and purity data in the PD can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the DOS-PD. Officially recognized compendial methods need not be summarized unless modifications have been made.

Although HPLC is normally considered the method of choice for determining API-related impurities, other chromatographic methods such as GC and thin-layer chromatography (TLC) can also be used, if appropriately validated. For determination of related substances, reference standards should normally be available for each of the identified impurities, particularly those known to be toxic and the concentration of the impurities should be quantitated against their own reference standards. Impurity standards may be obtained from pharmacopoeias (individual impurities or resolution mixtures), from commercial sources, or prepared in-house. It is considered acceptable to use the API as an external standard to estimate the levels of impurities, provided the response factors of those impurities are sufficiently close to that of the API, i.e., between 80 and 120 percent. In cases where the response factor is outside this range, it may still be acceptable to use the API, provided a correction factor is applied. Data to support calculation of the correction factor should be provided for an in-house method. Unspecified impurities may be quantitated using a solution of the API as the reference standard at a concentration corresponding to the limit established for individual unspecified impurities (e.g., 0.10%).

The system suitability tests (SSTs) represent an integral part of the method and are used to ensure the adequate performance of the chosen chromatographic system. As a minimum, HPLC and GC purity methods should include SSTs for resolution and repeatability. For HPLC methods to control API-related impurities, this is typically done using a solution of the API with a concentration corresponding to the limit for unspecified impurities. Resolution of the two closest eluting peaks is generally recommended. However, the choice of alternate peaks can be used if justified (e.g., choice of a toxic impurity).The method for repeatability test should include an acceptable number of replicate injections. HPLC assay methods should include SSTs for repeatability and in addition either peak asymmetry, theoretical plates or resolution. For thin layer chromatography (TLC)

methods, the SSTs should verify the ability of the system to separate and detect the analyte(s) (e.g., by applying a spot corresponding to the API at a concentration corresponding to the limit of unspecified impurities). [Reference: ICH Guideline Q2; WHO Technical Report Series, No. 943, Annex 3]

3.2.S.4.3 Validation of analytical procedures (name, manufacturer)

Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided.

Copies of the validation reports for the analytical procedures used to generate testing results, as well as those proposed for routine testing of the API by the FPP manufacturer should be provided.

Tables for summarizing a number of the different analytical procedures and validation information (e.g., HPLC assay/impurity methods, GC methods) can be found in the 2.3.R Regional information section of the DOS-PD (i.e., *2.3.R.2)*.These tables should be used to summarize the validation information of the analytical procedures *of the FPP manufacturer* for determination of residual solvents, assay, and purity of the API, in section 2.3.S.4.3 of the DOS-PD. The validation data for other methods used to generate assay and purity data in the PD can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the DOS-PD.

As recognized by stringent regulatory authorities and pharmacopoeias themselves, verification of compendial methods can be necessary. The compendial methods as published are typically validated based on an API or an FPP originating from a specific manufacturer. Different sources of the same API or FPP can contain impurities and/or degradation products that were not considered during the development of the monograph. Therefore, the monograph and compendial method should be demonstrated suitable to control the impurity profile of the API from the intended source(s).

In general, verification is not necessary for compendial API *assay* methods. However, specificity of a specific compendial assay method should be demonstrated if there are any potential impurities that are not specified in the compendial monograph. If an officially recognized compendial method is used to control API-related impurities that are not specified in the monograph, full validation of the method is expected with respect to those impurities.

If an officially recognized compendial standard is claimed and an in-house method is used in lieu of the compendial method (e.g., for assay or for specified impurities), equivalency of the in-house and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For impurity methods, the sample analyzed should be the API spiked with impurities at concentrations equivalent to their specification limits.
(Reference documents: ICH Q2)

3.2.S.4.4 Batch analyses (name, manufacturer)

Description of batches and results of batch analyses should be provided. The information provided should include batch number, batch size, date and production site of relevant API batches used in comparative bioavailability or biowaiver studies, preclinical and clinical data (if relevant), stability, pilot, scale-up and, if available, production-scale batches. This data is used to establish the specifications and evaluate consistency in API quality.

Analytical results should be provided from at least two batches of, at least, pilot-scale from each proposed manufacturing site of the API and should include the batch(es) used in the comparative bioavailability or biowaiver studies. A pilot-scale batch should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

Copies of the certificates of analysis, both from the API manufacturer(s) and the FPP manufacturer, should be provided for the profiled batches and any company responsible for generating the test results should be identified. The FPP manufacturer's test results should be summarized in the DOS-PD.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "all tests meet specifications." For quantitative tests (e.g., individual and total impurity tests and assay tests), it should be ensured that actual *numerical results* are provided rather than vague statements such as "within limits" or "conforms."

A discussion and justification should be provided for any incomplete analyses (e.g., results not tested according to the proposed specification).

(Reference documents: ICH Q3A, Q3C, Q6A)

3.2.S.4.5 Justification of specification (name, manufacturer)

Justification for the drug substance specification should be provided.

A discussion should be provided on the inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, differences from the officially recognized compendial standard(s), etc. If the officially recognized compendial methods have been modified or replaced, a discussion should be included.

The justification for certain tests, analytical procedures and acceptance criteria may have been discussed in other sections of the PD (e.g., impurities, particle size distribution) and does not need to be repeated here, although a cross-reference to their location should be provided. [Reference: ICH Guidelines Q3A, Q3C, Q6A; *officially recognized pharmacopoeia]*

3.2.S.5 Reference Standards or Materials (Name, Manufacturer)

Information should be provided on the reference standard(s) used to generate data in the PD, as well as those to be used by the FPP manufacturer in routine API and FPP testing.
The source(s) of the reference standards or materials used in the testing of the API should be provided (e.g., those used for the identification, purity, assay tests). These could be classified as *primary* or *secondary* reference standards.

A suitable primary reference standard should be obtained from an officially recognized pharmacopoeial source (e.g., Ph. Int., Ph. Eur., BP, USP, JP) where one exists, and the lot number should be provided. Where a pharmacopoeial standard is claimed for the API and/or the FPP, the primary reference standard should be obtained from that pharmacopoeia when available. Primary reference standards from officially recognized pharmacopoeial sources do not need further structural elucidation.

Otherwise, a primary standard may be a batch of the API that has been fully characterized (e.g., by IR, UV, NMR, MS analyses). Further purification techniques may be needed to render the material acceptable for use as a chemical reference standard. The purity requirements for a chemical reference substance depend upon its intended use. A chemical reference substance proposed for an identification test does not require meticulous purification, since the presence of a small percentage of impurities in the substance often has no noticeable effect on the test. On the other hand, chemical reference substances that are to be used in assays should possess a high degree of purity (such as 99.5% on the dried or water/solvent-free basis). Absolute content of the primary reference standard must be declared and should follow the scheme: 100% minus organic impurities (quantitated by an assay procedure, e.g., HPLC, DSC, etc.) minus inorganic impurities minus volatile impurities by loss on drying (or water content minus residual solvents).

A secondary (or in-house) reference standard can be used by establishing it against a suitable primary reference standard, e.g., by providing legible copies of the IR of the primary and secondary reference standards run concomitantly and by providing its certificate of analysis, including assay determined against the primary reference standard. A secondary reference standard is often characterized and evaluated for its intended purpose with additional procedures other than those used in routine testing (e.g., if additional solvents are used during the additional purification process that are not used for routine purposes). [Reference: ICH Guideline Q6A; WHO Technical Report Series, No. 943, Annex 3]

3.2.S.6 Container Closure System (Name, Manufacturer)

A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the API, including sorption to container and leaching, and/or safety of materials of construction. The WHO *Guidelines on packaging for pharmaceutical products* (WHO Technical Report Series, No. 902, Annex 9, 2002) and officially recognized pharmacopoeias should be consulted for recommendations on the packaging information for APIs.

Primary packaging components are those that are in direct contact with the API or FPP. The specifications for the primary packaging components should be provided and should include a specific test for identification (e.g., IR).

Copies of the labels applied on the secondary packaging of the API should be provided and should include the conditions of storage. In addition, the name and address of the manufacturer of the API should be stated on the container, regardless of whether relabeling is conducted at any stage during the API distribution process.

3.2.S.7 Stability (Name, Manufacturer)

3.2.S.7.1 Stability summary and conclusions (name, manufacturer)

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and re-test date or shelf-life, as appropriate.

The WHO Guidelines on Stability testing of active pharmaceutical ingredients and finished pharmaceutical products should be consulted for recommendations on the core stability data package.

As outlined in the WHO stability guidelines, the purpose of stability testing is to: “provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light.”

The tables in the DOS-PD template should be used to summarize the results from the stability studies and related information (e.g., conditions, testing parameters, conclusions, commitments).

Stress testing

As outlined in the ICH Q1A guidance document, stress testing of the API can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating

power of the analytical procedures used. The nature of the stress testing will depend on the individual API and the type of FPP involved.

Stress testing may be carried out on a single batch of the API. For examples of typical stress conditions, refer to WHO Technical Report Series, No. 1010, Annex 1010, Section 2.1.2, as well as, "A typical set of studies of the degradation paths of an active pharmaceutical ingredient," in WHO Technical Report Series, No. 929, Annex 5, Table A.1.

The object of stress testing is not to completely degrade the API, but to cause degradation to occur to a small extent, typically 10-30% loss of API by assay when compared with non-degraded API. This target is chosen so that some degradation occurs, but not enough to generate secondary products. For this reason, the conditions and duration may need to be varied when the API is especially susceptible to a particular stress factor. In the total absence of degradation products after 10 days, the API is considered stable under the particular stress condition.

The tables in the DOS-PD template should be used to summarize the results of the stress testing and should include the treatment conditions (e.g., temperatures, relative humidities, concentrations of solutions, durations) and the observations for the various test parameters (e.g., assay, degradation products). The discussion of results should highlight whether mass balance was observed.

Photostability testing should be an integral part of stress testing. The standard conditions are described in the ICH Q1B guidance document. If "protect from light" is stated in one of the officially recognized pharmacopoeia for the API, it is sufficient to state "protect from light" on labeling, in lieu of photostability studies, when the container closure system is shown to be light protective.

When available, it is acceptable to provide the relevant data published in the scientific literature (inter alia WHOPARs, EPARs) to support the identified degradation products and pathways.

Accelerated and long-term testing

Available information on the stability of the API under accelerated and long-term conditions should be provided, including information in the public domain or obtained from scientific literature. The source of the information should be identified.

The storage conditions and the lengths of studies chosen should be sufficient to cover storage and shipment. Refer to the WHO stability guidelines in WHO Technical Report Series, No. 1010, Annex 10, 2018.

The long-term storage conditions for APIs is either 25ºC±2ºC/60%±5%RH is acceptable; however, the preferred long-term storage conditions for APIs is either 30ºC±2ºC/65%±5%RH or 30ºC±2ºC/75%±5%RH. Alternative conditions should be

supported with appropriate evidence, which may include literature references or in-house studies, demonstrating that storage at 30ºC is inappropriate for the API. For APIs intended for storage in a refrigerator and those intended for storage in a freezer refer to the stability guideline, WHO Technical Report Series, No. 1010 Annex 10. APIs intended for storage below -20°C should be treated on a case-by-case basis.

To establish the re-test period, data should be provided on not less than three batches of, at least, pilot-scale. The batches should be manufactured by the same synthesis route as production batches and using a method of manufacture and procedure that simulates the final process to be used for production batches. The stability testing program and results should be summarized in the dossier and in the tables in the DOS-PD.

The information on the stability studies should include details such as storage conditions, batch number, batch size, container closure system, and completed (and proposed) test intervals. The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "all tests meet specifications." Ranges of analytical results where relevant and any trends that were observed should be included. For quantitative tests (e.g., individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements, such as "within limits" or "conforms." Where different from the methods described in S.4.2, descriptions and validation of the methodology used in stability studies should be provided.

The minimum data required at the time of submitting the dossier (in general) are:

Type	**Storage conduction**	**Minimum time (months)**
Accelerated	40°C ±2 °C /75±5%RH	6
Intermediate *	30 °C ± 2 °C/65% RH ± 5% RH	6
Long-term	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	12(for new API) or 6 (for existing API)

*Where long-term conditions are 30ºC±2ºC/65%±5%RH or 30ºC±2ºC/75%±5%RH, there is no intermediate condition.

For Active pharmaceutical ingredients intended for storage in a refrigerator:

Type	Storage conduction	Minimum time period covered by data at submission
Long-term	40°C ±2 °C /75±5%RH	12(for new API) or 6 (for existing API)
Accelerated*	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	6

*Whether accelerated stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ±5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe accelerated condition can be an alternative to storage testing at 25 °C/60% RH or 30 °C/65% RH.

Refer to WHO *Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products* (WHO Technical Report Series, No. 1010, Annex 10, 2018) for further information regarding the storage conditions, container closure system, test specifications and testing frequency.

Proposed storage statement and re-test period

A storage statement should be established for display on the label based on the stability evaluation of the API. The WHO stability guideline includes a number of recommended storage statements that should be used, when supported by the stability studies.

A re-test period should be derived from the stability information and should be displayed on the container label.

After this re-test period, a batch of API destined for use in the manufacture of an FPP could be re-tested and then, if in compliance with the specification, could be used immediately (e.g., within 30 days). If re-tested and found compliant, the batch does *not* receive an additional period corresponding to the time established for the re-test period. However, an API batch can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. For APIs known to be labile (e.g., certain antibiotics), it is more appropriate to establish a shelf-life rather than a re-test period. [Reference: ICH Guideline Q1A]

Limited extrapolation of the real time data from the long-term storage condition beyond the observed range to extend the re-test period can be undertaken at the time of assessment of the PD, if justified. Applicants should consult the ICH Q1E guidance document for further details on the evaluation and extrapolation of results from stability data (e.g., if significant change was not observed within six months at accelerated condition and the data show little or no variability, the proposed re-test period could be up to two times the period covered by the long-term data, but should not exceed the long-term data by 12 months).[Reference: ICH Guidelines Q1A, Q1B, Q1D, Q1E; WHO Technical Report Series, No. 1010, Annex 10]

3.2. S.7.2 Post-approval stability protocol and stability commitment (name, manufacturer)

The post-approval stability protocol and stability commitment either from API manufacturer or FPP manufacturer (whoever responsible for the study) should be provided.

Primary stability study commitment

When available long-term stability data on primary batches do not cover the proposed re-test, period granted at the time of assessment of the PD, a commitment should be made to continue the stability studies in order to firmly establish the re-test period. A written commitment (signed and dated) to continue long-term testing over the re-test period should be included in the dossier when relevant.

Commitment stability studies

The long-term stability studies for the *commitment batches* should be conducted through the proposed re-test period on at least three production batches. Where stability data was not provided for three production batches, a written commitment (signed and dated) should be included in the dossier.

The stability protocol for the *commitment batches* should be provided and should include, but not be limited to, the following parameters:

- number of batch(es) and different batch sizes, if applicable;
- relevant physical, chemical, microbiological, and biological test methods;
- acceptance criteria;
- reference to test methods;
- description of the container closure system(s);
- testing frequency;
- description of the conditions of storage (standardized conditions for long-term testing as described in this Guideline and consistent with the API labeling, should be used); and,
- Other applicable parameters specific to the API.

Ongoing stability studies

The stability of the API should be monitored according to a continuous and appropriate program that will permit the detection of any stability issue (e.g., changes in levels of degradation products). The purpose of the ongoing stability program is to monitor the API and to determine that the API remains and can be expected to remain within the re-test period in all future batches.

At least one production batch per year of API (unless none is produced during that year) should be added to the stability monitoring program and generally should be tested at least every 6 months in the first year and then annually to confirm the stability. In certain situations, additional batches should be included. A written commitment (signed and dated) from API manufacturer for ongoing stability studies should be included in the dossier.

Refer to WHO Technical Report Series, No. 1010, 2019, Annex 10, Section 2.1.11 for further information on ongoing stability studies.

Any differences between the stability protocols used for the primary batches and those proposed for the commitment batches or ongoing batches should be scientifically justified.
Reference documents: ICH Q1A, Q1B, Q1D, Q1E, WHO Technical Report Series, No. 1010, 2019, Annex 10.

3.2.S.7.3 Stability data (name, manufacturer)

Results of the stability studies (e.g. forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.
The actual stability results used to support the proposed re-test period should be included in the dossier. The result should be presented in an appropriate format such as tabular, graphical, or narrative description. Information on the analytical procedures used to generate the data and validation of these procedures should be included. For quantitative tests (e.g., individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms."[Reference: ICH Guidelines Q1A, Q1B, Q1D, Q1E, Q2; WHO Technical Report Series, No. 1010, Annex 10]

3.2. P Drug Product (or Finished Pharmaceutical Product (FPP)) (Name, Dosage Form)

3.2.P.1 Description and Composition of the FPP (Name, Dosage Form)

A description of the FPP and its composition should be provided. The information provided should include, for example:

- **Description of the dosage form**

  The description of the FPP should include the physical description, available strengths, release mechanism (e.g., immediate, modified (delayed or extended)), as well as any other distinguishable characteristics e.g.

  "The proposed XYZ 50 mg dispersible tablets are available as white, oval, film-coated tablets, debossed with '50' on one side and a break line on the other side. The proposed ABC 100 mg tablets are available as yellow, round, film-coated tablets, debossed with '100' on one side and plain on the other side."

- **Composition of the dosage form**

  Composition of the dosage form, and their amounts on a per unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications) should be provided.

  The tables in the DOS-PD template should be used to summarize the composition of the FPP and express the quantity of each component on a per unit basis (e.g., mg per tablet, mg per ml, mg per vial) and percentage basis, including a statement of the

total weight or measure of the dosage unit. The individual components for mixtures prepared in-house (e.g., coatings) should be included in the tables, where applicable.

All components used in the manufacturing process should be included, including those that may not be added to every batch (e.g., acid and alkali), those that may be removed during processing (e.g., solvents), and any others (e.g., nitrogen, silicon for stoppers). If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g., "1 mg of active ingredient base=1.075 mg active ingredient hydrochloride"). All overages should be clearly indicated (e.g., "contains 2% overage of the API to compensate for manufacturing losses").

The components should be declared by their proper or common names, quality standards (e.g., Ph.Int., Ph.Eur., BP, USP, JP, House) and, if applicable, their grades (e.g., "Microcrystalline Cellulose NF (PH 102)") and special technical characteristics (e.g., lyophilized, micronized, solubilized, emulsified).

The function of each component (e.g., diluent/filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent, antimicrobial preservative) should be stated. If an excipient performs multiple functions, the predominant function should be indicated.

The qualitative composition, including solvents, should be provided for all proprietary components or blends (e.g., capsule shells, coloring blends, imprinting inks). This information (excluding the solvents) is to be listed in the product information (e.g., summary of product characteristics, labeling, and package leaflet).

- **Description of accompanying reconstitution diluent(s)**
  For FPPs supplied with reconstitution diluent(s) that are commercially available or have been assessed and considered acceptable in connection with another PD with the Authority, a brief description of the reconstitution diluents(s) should be provided.

  For FPPs supplied with reconstitution diluent(s) that are not commercially available or have not been assessed and considered acceptable in connection with another PD with the Authority, information on the diluent(s) should be provided in a separate FPP portion ("3.2.P"), as appropriate.

- **Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable**
  The container closure used for the FPP (and accompanying reconstitution diluent, if applicable) should be briefly described, with further details provided under 3.2.P.7 Container closure system, e.g.:

  > "The product is available in HDPE bottles with polypropylene caps (in sizes of 100's, 500's and 1000's) and in PVC/Aluminum foil unit dose blisters (in packages of 100's (cards of 5x2, 10 cards per package))."

[Refer ICH Q6A]

3.2.P.2 Pharmaceutical Development (Name, Dosage Form)

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes, and usage instructions are appropriate for the purpose specified in the product dossier. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and FPP quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the product dossier.

Pharmaceutical development information should include, at a minimum:

- definition of the quality target product profile (QTPP) as it relates to quality, safety and efficacy, considering, for example, the route of administration, dosage form, bioavailability, strength, and stability;
- identification of the potential critical quality attributes (CQAs) of the FPP so as to adequately control the product characteristics that could have an impact on quality;
- discussion of the potential CQAs of the API(s), excipients, and container closure system(s), including the selection of the type, grade, and amount to deliver drug product of the desired quality; and,
- discussion of the selection criteria for the manufacturing process and the control strategy required to manufacture commercial lots meeting the QTPP in a consistent manner.

These features should be discussed as part of the product development using the principles of risk management over the entire lifecycle of the product (ICH Q8).

For a discussion of additional pharmaceutical development issues specific to the development of FDCs, reference should be made to WHO Technical Report Series, No. 929, 2005, Annex 5, section 6.3.2.

[Reference documents: ICH Q6A, Q8, Q9, Q10, WHO Technical Report Series 970, 2012, Annex 3]

3.2.P.2.1 Components of the FPP (name, dosage form)

3.2.P.2.1.1 Active pharmaceutical ingredient (name, dosage form)

The compatibility of the API with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics of the API (e.g., water content, solubility, particle size distribution, polymorphic, or solid-state form) that can influence the performance of the FPP should be discussed. For fixed-dose combinations, the compatibility of APIs with each other should be discussed.

Physicochemical characteristics of the API may influence both the manufacturing capability and the performance of the FPP.

Guidance on compatibility studies is provided in appendix 3 of the WHO Guidelines for registration of fixed-dose combination medicinal products (WHO Technical Report Series, No. 929, 2005, Annex 5). In addition to visual examination, chromatographic results (assay, purity) are required to demonstrate API–API and API–excipient compatibility. In general, API–excipient compatibility is not required to be established for specific excipients when evidence is provided (e.g., SmPC or product leaflet) that the excipients are present in the comparator product.

3.2.P.2.1.2 Excipients (name, dosage form)

When choosing excipients, those with a compendial monograph are generally preferred and may be required in certain jurisdictions. Other resources are available for information on acceptable excipients and their concentrations, such as the FDA IIG list and the *Handbook of Pharmaceutical Excipients*. Use of excipients in concentrations outside of established ranges are discouraged and generally requires justification. In addition, available guidelines should be referenced which address particular excipients to be avoided, for example, azocolorants listed in European Medicines Agency's (EMA) Guideline CPMP/463/00, and the Colorcon Regulatory Information Sheet on AZO and Non-AZO Colorants. Other guidelines, such as the WHO Guidelines on development of paediatric medicines (WHO Technical Report Series, No. 970, 2012, Annex 5)
may provide useful general Guidance in this regard.

Ranges or alternates for excipients are normally not accepted, unless supported by appropriate process validation data. Where relevant, compatibility study results (e.g., compatibility of a primary or secondary amine API with lactose) should be included to justify the choice of excipients. Specific details should be provided where necessary (e.g., use of potato or corn starch).

Where antioxidants are included in the formulation, the effectiveness of the proposed concentration of the antioxidant as well as its safety should be justified and verified by appropriate studies.

Antimicrobial preservatives are discussed in 3.2.P.2.5.

3.2.P.2.2 Finished pharmaceutical product (name, dosage form)

3.2.P.2.2.1 Formulation development (name, dosage form)

A brief summary describing the development of the FPP should be provided, taking into consideration the proposed route of administration and usage. The differences between the comparative bioavailability or biowaiver formulations and the formulation (i.e., composition) described in 3.2.P.1 should be discussed. Results from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed, when appropriate.

An *established multisource product* is defined as one that has been marketed by the applicant or manufacturer associated with the dossier for at least five years and for which at least 10 production batches were produced over the previous year, or, if less than 10 batches were produced in the previous year, not less than 25 batches were produced in the previous three years. For products that meet the criteria of an *established multisource product,* all sections of 3.2.P.2.2.1 of the dossier and DOS-PD should be completed, with the exception of 2.3.P.2.2.1 (a).In addition, a product quality review should be provided as outlined in Appendix 1.

The requirements for bioequivalence studies should be taken into consideration, for example, when formulating multiple strengths and/or when the product(s) may be eligible for a biowaiver. WHO reference documents (e.g. WHO Technical Report Series, No. 992, 2015, Annex 7) may be consulted. Product clinical information, including bioequivalence and biowaiver justification, should be documented under Module 5.

Product scoring may be recommended or required, for example, when division into fractional doses may be necessary according to approved posology.

If the proposed FPP is a functionally scored tablet, a study should be undertaken to ensure the uniformity of dose in the tablet fragments. The data provided in the PD should include a description of the test method, individual values, mean and relative standard deviation (RSD) of the results. Uniformity testing (i.e. content uniformity for split portions containing less than 5 mg or less than 5% of the weight of the dosage unit portion, or mass uniformity for other situations) should be performed on each split portion from a minimum of 10 randomly selected whole tablets. As an illustrative example, the number of units (i.e. the splits) would be 10 halves for bisected tablets (one half of each tablet is retained for the test) or 10 quarters for quadrisected tablets (one quarter of each tablet is retained for the test). At least one batch of each strength should be tested. Ideally, the study should cover a range of the hardness values. The splitting of the tablets should be performed in a manner that would be representative of that used by the consumer (e.g. manually split by hand). The uniformity test on split portions can be demonstrated on a one-time basis and does not need to be added to the FPP specification(s). The tablet description in the FPP specification and in the product information (e.g. summary of product characteristics, labelling, package leaflet) should reflect the presence of a score.

If splitting of a tablet is intended for a paediatric dose, a demonstration of content uniformity of tablet fragments may be required.

Where relevant, labelling should state that the score line is only to facilitate breaking for ease of swallowing and not to divide tablets into equal doses.

Additional quality data may be required to support special dosing instructions (for example, crushing) stated in product information.

In vitro dissolution or drug release

A discussion should be included as to how the development of the formulation relates to development of the dissolution method(s) and the generation of the dissolution profile.

The results of studies justifying the choice of in vitro dissolution or drug release conditions (e.g., apparatus, rotation speed, medium) should be provided. Data should also be submitted to demonstrate whether the method is sensitive to changes in manufacturing processes, and/or changes in grades, and/or amounts of critical excipients and particle size, where relevant. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters. Use of a single point test or a dissolution range should be justified based on the solubility and/or biopharmaceutical classification of the API.

For slower dissolving immediate-release products (e.g., Q=80% in 90 minutes), a second-time point may be warranted (e.g., Q=60% in 45 minutes).

Delayed release (enteric coated) products are intended to resist gastric fluid but disintegrate in intestinal fluid; therefore, dissolution should include acid and buffer phases with separate criteria for each. Refer to compendial monographs for examples.

Modified-release FPPs should have a meaningful in vitro release rate (dissolution) test that is used for routine quality control. Preferably this test should possess in vitro–in vivo correlation. Results demonstrating the effect of pH on the dissolution profile should be submitted if appropriate for the type of dosage form.

For extended-release FPPs, the testing conditions should be set to cover the entire time period of expected release (e.g., at least three test intervals chosen for a 12-hour release and additional test intervals for longer duration of release). One of the test points should be at the early stage of drug release (e.g., within the first hour) to demonstrate absence of dose dumping. At each test period, upper and lower limits should be set for individual units. Generally, the acceptance range at each intermediate test point should not exceed 20% or ±10% of the targeted value. Dissolution results should be submitted for several lots, including those lots used for pharmacokinetic and bioavailability or biowaiver studies. Recommendations for conducting and assessing comparative dissolution profiles can be found in Appendix 3.

3.2.P.2.2.2 Overages (name, dosage form)

Any overages in the formulation(s) described in 3.2.P.1 should be justified.

Justification of an overage to compensate for loss during manufacture should be provided, including the step(s) where the loss occurs, the reasons for the loss, and batch analysis release data (assay results).

Overages for the sole purpose of extending the shelf-life of the FPP are generally not acceptable.

3.2.P.2.2.3 Physicochemical and biological properties (name, dosage form)

Parameters relevant to the performance of the FPP, such as pH, ionic strength, dissolution, re-dispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity, should be addressed.

When polymorphism is an issue for the API as discussed in 3.2.S.3.1, it may be necessary to provide information on the form present in the FPP, for example, when the manufacturing process may affect the form. Such studies may not be necessary when sufficient information has been provided on the polymorphism observed during API stability studies.

3.2.P.2.3 Manufacturing process development (name, dosage form)

The selection and optimization of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.

Where relevant, justification for the selection of aseptic processing or other sterilization methods over terminal sterilization should be provided.

Differences between the manufacturing process used to produce comparative bioavailability or biowaiver batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.

For products that meet the criteria of an *established multisource product* in order to fulfill the requirements of section 3.2.P.2.3, section 2.3.P.2.3 (b) of the DOS-PD should be completed and a product quality review should be submitted as outlined in Appendix 1.

The rationale for choosing the particular pharmaceutical product (e.g., dosage form, delivery system) should be provided. The scientific rationale for the choice of the manufacturing, filling, and packaging processes that can influence FPP quality and performance should be explained (e.g., wet granulation using high shear granulator).API stress study results may be included in the rationale. Any developmental work undertaken to protect the FPP from deterioration should also be included (e.g., protection from light or moisture).

The scientific rationale for the selection, optimization, and scale-up of the manufacturing process described in 3.2.P.3.3 should be explained, in particular, the critical aspects (e.g., rate of addition of granulating fluid, massing time, granulation end-point). A discussion of the critical process parameters (CPP), controls, and robustness with respect to the QTPP and CQA of the product should be included. [Reference: ICH Guideline Q8]

3.2.P.2.4 Container closure system (name, dosage form)

The suitability of the container closure system (described in 3.2.P.7) used for the storage, transportation (shipping), and use of the FPP should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and

leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the FPP).

Testing requirements to verify the suitability of the container closure system contact material(s) depend on the dosage form and route of administration. The pharmacopoeias provide standards that are required for packaging materials, including, for example, the following:

Container type	**Pharmacopoeial standards**
Glass containers:	USP <660>
	Ph.Eur. 3.2.1
Plastic containers:	Ph.Eur. 3.2.2, 3.2.2.1
	USP <661>, <671>
Rubber/elastomeric closures	USP <381>
	Ph.Eur. 3.2.9

The following table outlines the general recommendations for the various dosage forms for one-time studies to establish the suitability of the container closure system contact materials.

	Solid oral products	**Oral liquid and topical products**	**Sterile products (including ophthalmics)**
Description of any additional treatments*	X	X	X (sterilization and depyrogenation of the components)
e.g., USP <661> Containers – plastics**	X	X	X (includes e.g., USP <87>/<88> tests**)
e.g., USP <671> Containers – performance testing**	X	X	X
e.g., USP <381> Elastomeric closures for injections**	---	---	X (includes e.g., USP <87>/<88> tests**)

*e.g., coating of tubes, siliconization of rubber stoppers, sulphur treatment of ampoules/vials
X = information should be submitted
--- = information does not need to be submitted
**Note that equivalent tests of other officially recognized pharmacopoeia may be substituted.

For solid oral dosage forms and solid APIs, compliance with regulations on plastic materials that come into contact with food (for example (EU) No. 10/2011) can be considered acceptable in lieu of extraction studies.

The suitability of the container closure system used for the storage, transportation (shipping) and use of any intermediate/in-process products (e.g., premixes, bulk FPP) should also be discussed.

A device is required to be included with the container closure system for oral liquids or solids (e.g., solutions, emulsions, suspensions and powders/granules for such reconstitution), any time the package provides for multiple doses.

In accordance with the Ph.Int, general chapter Liquid preparations for oral use: "Each dose from a multidose container is administered by means of a device suitable for measuring the prescribed volume. The device is usually a spoon or a cup for volumes of 5 ml or multiples thereof, or an oral syringe for other volumes or, for oral drops, a suitable dropper." For a device accompanying a multi-dose container, the results of a study should be provided demonstrating the reproducibility of the device (e.g., consistent delivery of the intended volume), generally at the lowest intended dose. A sample of the device should be provided in Module 1.

3.2.P.2.5 Microbiological attributes (name, dosage form)

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

Where an antimicrobial preservative is included in the formulation, the amount used should be justified by submission of results of the product formulated with different concentrations of the preservative(s) to demonstrate the least necessary but still effective concentration. The effectiveness of the agent should be justified and verified by appropriate studies (e.g., USP or Ph. Eur. general chapters on antimicrobial preservatives) using a batch of the FPP. If the lower bound limit for the proposed acceptance criterion for the assay of the preservative is less than 90.0%, the effectiveness of the agent should be established with a batch of the FPP containing a concentration of the antimicrobial preservative corresponding to the lower proposed acceptance criteria.

As outlined in the WHO stability guidelines (WHO Technical Report Series, No. 1010, 2019, Annex 10), a single primary stability batch of the FPP should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf-life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

3.2.P.2.6 Compatibility (name, dosage form)

The compatibility of the FPP with reconstitution diluent(s) or dosage devices (e.g., precipitation of API in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labeling.

Where a device is required for oral liquids or solids (e.g., solutions, emulsions, suspensions and powders/granules for such reconstitution) that are intended to be administered

immediately after being added to the device, the compatibility studies mentioned in this Guideline are not required.

Where sterile, reconstituted products are to be further diluted, compatibility should be demonstrated with all diluents over the range of dilution proposed in the labeling. These studies should preferably be conducted on aged samples. Where the labeling does not specify the type of containers, compatibility (with respect to parameters such as appearance, pH, assay, levels of individual and total degradation products, sub visible particulate matter, and extractables from the packaging components) should be demonstrated in glass, PVC, and polyolefin containers. However, if one or more containers are identified in the labeling, compatibility of admixtures needs to be demonstrated only in the specified containers.

Studies should cover the duration of storage reported in the labeling (e.g., 24 hours under controlled room temperature and 72 hours under refrigeration). Where the labeling specifies co-administration with other FPPs, compatibility should be demonstrated with respect to the principal FPP as well as the co-administered FPP (i.e., in addition to other aforementioned parameters for the mixture, the assay and degradation levels of each co-administered FPP should be reported).

3.2.P.3 Manufacture (name, dosage form)

3.2.P.3.1 Manufacturer(s) (name, dosage form)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

The facilities involved in the manufacturing, packaging, labeling and testing should be listed. If certain companies are responsible only for specific steps (e.g., manufacturing of an intermediate) such should be clearly indicated in the dossier.

The list of manufacturers/companies should specify the *actual addresses* of production or manufacturing site(s) involved (including block(s) and unit(s)), rather than the administrative offices.

For a mixture of an API with an excipient, the blending of the API with the excipient is considered to be the critical step in the manufacture of the final product and therefore the mixture does not fall under the definition of an API. The only exceptions are in the cases where the API cannot exist on its own. Similarly, for a mixture of APIs, the blending of the APIs is considered to be the critical step in the manufacture of the final product. Sites for such manufacturing steps should be included in this section.

A valid manufacturing authorization for pharmaceutical production is generally required and a marketing authorization may be required to demonstrate that the product is registered or licensed in accordance with national requirements.

For each site where the major production step(s) are carried out, when applicable, attach a WHO-type certificate of product issued by a competent authority in terms of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (refer Module 1).

Justification for any differences to the product in the country or countries issuing the WHO-type certificate(s).

When there are differences between the product for which this application is submitted and that marketed in the country/countries which provided the WHO-type certificate(s), provide data to support the applicability of the certificate(s) despite the differences. Depending on the case, it may be necessary to provide validation data for differences in site of manufacture, specifications, formulation, etc. Note that only minor differences are likely to be acceptable.

Regulatory situation in other countries

The countries should be listed in which this product has been granted a marketing authorization, this product has been withdrawn from the market and/or this application for marketing has been rejected, deferred, or withdrawn.

Reference documents: WHO Technical Report Series, No. 961, 2011, Annex 3 and WHO Technical Report Series, No. 957, 2010, Annex 5.

3.2.P.3.2 Batch formula (name, dosage form)

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards. Applicant should declare the proposed batch size(s) of the product manufactured for the supply to the Ethiopian market.

The tables in the DOS-PD template should be used to summarize the batch formula of the FPP *for each proposed commercial batch size* and express the quantity of each component on a per batch basis, including a statement of the total weight or measure of the batch.

All components used in the manufacturing process should be included, including those that may not be added to every batch (e.g., acid and alkali), those that may be removed during processing (e.g., solvents) and any others (e.g., nitrogen, silicon for stoppers). If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g., “1 kg of active ingredient base = 1.075 kg active ingredient hydrochloride”). All overages should be clearly indicated (e.g., “Contains 5 kg (corresponding to 2%) overage of the API to compensate for manufacturing losses”).

The components should be declared by their proper or common names, quality standards (e.g., Ph.Int., Ph.Eur., BP, USP, JP, House) and, if applicable, their grades (e.g., "Microcrystalline Cellulose NF (PH 102)") and special technical characteristics (e.g., lyophilized, micronized, solubilized, emulsified).

3.2.P.3.3 Description of manufacturing process and process controls (name, dosage form)

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative description of the manufacturing process, including packaging that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogenizer) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section 3.2.P.3.4. In certain cases, environmental conditions (e.g., low humidity for an effervescent product) should be stated.

The maximum holding time for bulk FPP prior to final packaging should be stated. The holding time should be supported by the submission of stability data, if longer than 30 days. For an aseptically processed sterile product, the holding of the filtered product and sterilized component prior to filling should be under UDLAF (Class A) system and filling should be done immediately within 24hrs.

Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced to development section or filed in this section

The information above should be summarized in the DOS-PD template and should reflect the production of the proposed commercial batches.
For the manufacture of sterile products, the class (e.g., class A, B, C, etc.) of the areas should be stated for each activity (e.g., compounding, filling, sealing, etc.), as well as the sterilization parameters for equipment, container/closure, terminal sterilization etc.
[Reference documents : ICH Q8, Q9, Q10]

3.2.P.3.4 Controls of critical steps and intermediates (name, dosage form)

Critical Steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the manufacturing process, to ensure that the process is controlled.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Examples of applicable in-process controls include:

- granulations: moisture (limits expressed as a range), blend uniformity (e.g., low dose tablets), bulk and tapped densities, particle size distribution;
- solid oral products: average weight, weight variation, hardness, thickness, friability, and disintegration checked periodically throughout compression, weight gain during coating;
- semi-solids: viscosity, homogeneity, pH;
- transdermal dosage forms: assay of API-adhesive mixture, weight per area of coated patch without backing;
- metered dose inhalers: fill weight/volume, leak testing, valve delivery;
- dry powder inhalers: assay of API-excipient blend, moisture, weight variation of individually contained doses such as capsules or blisters;
- liquids: pH, specific gravity, clarity of solutions; and,
- parenteral: appearance, clarity, fill volume/weight, pH, filter integrity tests, particulate matter, leak testing of ampoules.

[Reference: ICH Guidelines Q2, Q6A, Q8, Q9, Q10; WHO Technical Report Series, No. 929, Annex 5]

3.2.P.3.5 Process validation and/or evaluation (name, dosage form)

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilization process or aseptic processing or filling). Viral safety evaluation should be provided in 3.2A.2, if necessary.

For products that meet the criteria of an *established multisource product,* a product quality review as outlined in Appendix 1 may be submitted in lieu of the information below.

The following information should be provided for all other products:

a) a copy of the *process validation protocol*, specific to this FPP, that identifies the critical equipment and process parameters that can affect the quality of the FPP and defines testing parameters, sampling plans, analytical procedures and acceptance criteria;
b) a *commitment* that three consecutive, production-scale batches of this FPP will be subjected to *prospective validation* in accordance with the above protocol. The applicant should submit a written commitment that information from these studies will be available for verification after registration by the Authority inspection team; and,
c) if the process validation studies have already been conducted (e.g., for sterile products), a copy of the *process validation report* should be provided in the PD in lieu of (a) and (b) above.

One of the most practical forms of process validation, mainly for non-sterile products, is the final testing of the product to an extent greater than that required in routine quality control. It may involve extensive sampling, far beyond that called for in routine quality control and testing to normal quality control specifications and often for certain parameters only. Thus, for instance, several hundred tablets per batch may be weighed to determine unit dose uniformity. The results are then treated statistically to verify the "normality" of the distribution and to determine the standard deviation from the average weight. Confidence limits for individual results and for batch homogeneity are also estimated. Strong assurance is provided that samples taken at random will meet regulatory requirements if the confidence limits are well within compendial specifications.

Similarly, extensive sampling and testing may be performed with regard to any quality requirements. In addition, intermediate stages may be validated in the same way, e.g., dozens of samples may be assayed individually to validate mixing or granulation stages of low-dose tablet production by using the content uniformity test. Products (intermediate or final) may occasionally be tested for non-routine characteristics. Thus, sub visual particulate matter in parenteral preparations may be determined by means of electronic devices, or tablets/capsules tested for dissolution profile, if such tests are not performed on every batch.

Where ranges of batch sizes are proposed, it should be shown that variations in batch size would not adversely alter the characteristics of the finished product. It is envisaged that those parameters listed in the following validation scheme will need to be re-validated once further scale-up is proposed after registration.

The process validation protocol should include inter alia the following:

- a reference to the current master production document;
- a discussion of the critical equipment;
- the process parameters that can affect the quality of the FPP (critical process parameters (CPPs)), including challenge experiments and failure mode operation;
- details of the sampling—sampling points, stages of sampling, methods of sampling, and the sampling plans (including schematics of blender/storage bins for uniformity testing of the final blend);
- the testing parameters/acceptance criteria including in-process and release specifications and including comparative dissolution profiles of validation batches against the batch(es) used in the bioavailability or biowaiver studies;
- the analytical procedures or a reference to appropriate section(s) of the dossier;
- the methods for recording/evaluating results; and,
- the proposed timeframe for completion of the protocol.

The manufacture of sterile FPPs needs a well-controlled manufacturing area (e.g., a strictly controlled environment, highly reliable procedures, and appropriate in-process controls). A detailed description of these conditions, procedures and controls should be provided, together with actual copies of the following standard operating procedures:

a) washing, treatment, sterilizing, and depyrogenating of containers, closures, and equipment;
b) filtration of solutions;
c) lyophilization process;
d) leaker test of filled and sealed ampoules;
e) final inspection of the product;
f) sterilization cycle; and,
g) routine environmental monitoring and media fill validation exercise.

The sterilization process used to destroy or remove microorganisms is probably the single most important process in the manufacture of parenteral FPPs. The process can make use of moist heat (e.g., steam), dry heat, filtration, gaseous sterilization (e.g., ethylene oxide), or radiation. It should be noted that terminal steam sterilization, when practical, is considered to be the method of choice to ensure sterility of the final FPP. Therefore, scientific justification for selecting any other method of sterilization should be provided.

The sterilization process should be described in detail and evidence should be provided to confirm that it will produce a sterile product with a high degree of reliability and that the physical and chemical properties as well as the safety of the FPP will not be affected. Details, such as F_o range, temperature range, and peak dwell time for an FPP and the container closure should be provided. Although standard autoclaving cycles of 121°C for 15 minutes or more would not need a detailed rationale; such justifications should be provided for reduced temperature cycles or elevated temperature cycles with shortened exposure times. If ethylene oxide is used, studies and acceptance criteria should control the levels of residual ethylene oxide and related compounds.

Filters used should be validated with respect to pore size, compatibility with the product, absence of extractable, and adsorption of the API or any of the components.

For the validation of aseptic filling of parenteral products that cannot be terminally sterilized, simulation process trials should be conducted. This involves filling ampoules with culture media under normal conditions, followed by incubation and control of microbial growth. A level of contamination of less than 0.1% is considered to be acceptable. [Reference: ICH Guidelines Q8, Q9, Q10; WHO Technical Report Series, Nos. 961(Annex 3), 902 and 908]

3.2.P.4 Control of Excipients (Name, Dosage Form)

3.2.P.4.1 Specifications (name, dosage form)

The specifications from the applicant or the FPP manufacturer should be provided for all excipients, including those that may not be added to every batch (e.g., acid and alkali), those that do not appear in the final FPP (e.g., solvents) and any others used in the manufacturing process (e.g., nitrogen, silicon for stoppers).

If the standard claimed for an excipient is an officially recognized compendial standard, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the officially recognized compendial monograph.

If the standard claimed for an excipient is a non-compendial standard (e.g., House standard) or includes tests that are supplementary to those appearing in the officially recognized compendial monograph, a copy of the specification for the excipient should be provided.
In general, excipients with an officially-recognized pharmacopoeial monograph should be used. Exceptions should be justified.
For excipients of natural origin, microbial limit testing should be included in the specifications. Skip testing is acceptable, if justified (submission of acceptable results of five production batches).

For oils of plant origin (e.g., soy bean oil, peanut oil), the absence of aflatoxins or biocides should be demonstrated.

The colors permitted for use are limited to those listed in the "Japanese pharmaceutical excipients," the EU "List of permitted food colors," and the US FDA "Inactive ingredient guide." For proprietary mixtures, the supplier's product sheet with the qualitative formulation should be submitted, in addition to the FPP manufacturer's specifications for the product, including identification testing.

For flavors, the qualitative composition should be submitted, as well as a declaration that the excipients comply with foodstuff regulations (e.g., US FDA or EU).

Information that is considered confidential may be submitted directly to the Authority by the supplier with reference to the specific related product.

Other certifications of at-risk components may be required on a case-by-case basis.

If additional purification is undertaken on commercially available excipients, details of the process of purification and modified specifications should be submitted.
Reference documents: ICH Q6A

3.2.P.4.2 Analytical procedures (name, dosage form)

The analytical procedures used for testing the excipients should be provided, where appropriate.

Copies of analytical procedures from officially recognized compendial monographs do not need to be submitted.

Reference documents: ICH Q2

3.2.P.4.3 Validation of analytical procedures (name, dosage form)

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.

Copies of analytical validation information are generally not submitted for the testing of excipients, with the exception of the validation of in-house methods where appropriate.

Reference documents: ICH Q2

3.2.P.4.4 Justification of specifications (name, dosage form)

Justification for the proposed excipient specifications should be provided, where appropriate.

A discussion of the tests that are supplementary to those appearing in the officially recognized compendial monograph should be provided.

3.2.P.4.5 Excipients of human or animal origin (name, dosage form)

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications, description of the testing performed, viral safety data). For more detail, see Section 3.2.A.2.

The following excipients should be addressed in this section: gelatin, phosphates, stearic acid, magnesium stearate and other stearates. If from plant origin a declaration to this effect will suffice.

For these excipients from animal origin, a letter of attestation should be provided confirming that the excipients used to manufacture the FPP are *without* risk of transmitting agents of animal spongiform encephalopathies.

Materials of animal origin should be avoided whenever possible.

When available, a CEP demonstrating TSE-compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module 1. [Reference: ICH Guidelines Q5A, Q5D, Q6B; WHO Technical Report Series, No. 908, Annex 1]

3.2.P.4.6 Novel excipients (name, dosage form)

For excipient(s) used for the first time in an FPP or by a new route of administration, full details of manufacture, characterization, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the API and/or FPP intended purpose. (Details should be provided in 3.2.A.3).

The Authority may choose not to accept the use of novel excipients in submitted PDs. For the purpose of these guidelines, a novel excipient is one that has not been used (at a

similar level and by the same route of administration) in a product approved by an SRA or WHO. If novel excipients are accepted, full information should be provided in 3.2.A.3.

3.2.P.5 Control of FPP (name, dosage form)

3.2.P.5.1 Specification(s) (name, dosage form)

The specification(s) for the FPP should be provided. As defined in ICH's Q6A guideline, a specification is:

> "a list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which an API or FPP should conform to be considered acceptable for its intended use. 'Conformance to specifications' means that the API and /or FPP, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities."

A copy of the FPP specification(s) from the applicant (as well as the company responsible for the batch release of the FPP, if different from the applicant), dated and signed by authorized personnel (i.e., the person in charge of the quality control or quality assurance department) should be provided in the PD. Two separate sets of specifications may be set out: after packaging of the FPP (release) and shelf life monitoring.

The specifications should be summarized according to the tables in the DOS-PD template including the tests, acceptance criteria and analytical procedures (including types, sources and versions for the methods):

- the *standard* declared by the applicant could be an officially recognized compendial standard (e.g., Ph.Int., BP, USP, JP) or a in house (manufacturer's) standard;
- the *specification reference number and version (e.g., revision number and/or date)* should be provided for version control purposes; and,
- for the analytical procedures, the *type* should indicate the kind of analytical procedure used (e.g., visual, IR, UV, HPLC), the *source* refers to the origin of the analytical procedure (e.g., Ph.Int., Ph.Eur., BP, USP, JP, in-house), and the *version (e.g., code number/version/date)* should be provided for version control purposes.

Specifications should include, at minimum, tests for appearance, identification, assay, purity, pharmaceutical tests (e.g., dissolution), physical tests (e.g., loss on drying, hardness, friability, particle size, apparent density), uniformity of dosage units, identification of coloring materials, identification and assay of antimicrobial or chemical preservatives (e.g., antioxidants), and microbial limit tests.

The following information provides guidance for specific tests:

- fixed-dose combination FPPs (FDC-FPPs):
  - analytical methods that can distinguish each API in the presence of the other API(s) should be developed and validated,

  - acceptance criteria for degradation products should be established with reference to the API they are derived from. If an impurity results from a chemical reaction between two or more APIs, its acceptance limits should be calculated with reference to the worst case (the API with the smaller area under the curve). Alternatively, the content of such impurities could be calculated in relation to their reference standards,
  - a test and limit for content uniformity is required for each API present in the FPP at less than 5 mg or less than 5% of the weight of the dosage unit, [when any one API is present at less than 5 mg or less than 5% of the weight of the dosage unit, a test and limit for content uniformity is required for each API in the FPP, or as per the official monograph stated e.g. when any one API is present at less than 25 mg or less than 25% of the weight of the dosage unit, a test and limit for content uniformity is required for each API in the FPP]
  - for the API(s) present at greater than or equal to 5 mg and greater than or equal to 5% of the weight of the dosage unit, a test and limit for weight variation may be established in lieu of content uniformity testing; [when all APIs are present at equal or greater than 5 mg and equal or greater than 5% of the weight of the dosage unit, a test and limit for weight variation may be established for the FPP, in lieu of content uniformity testing; or as per the official monograph stated eg when any one API is present at less than 25 mg or less than 25% of the weight of the dosage unit, a test and limit for content uniformity is required for each API in the FPP]
- modified-release products: a meaningful API release method;
- inhalation and nasal products: consistency of delivered dose (throughout the use of the product), particle or droplet size distribution profiles (comparable to the product used in in-vivo studies, where applicable) and if applicable for the dosage form, moisture content, leak rate, microbial limits, preservative assay, sterility and weight loss;
- suppositories: uniformity of dosage units, melting point;
- transdermal dosage forms: peel or shear force, mean weight per unit area, dissolution; and,
- sterile: sterility, endotoxin, particle count.

Unless there is appropriate justification, the acceptable limit for the API content of the FPP in the release specifications is ± 5% of the label claim (i.e., 95.0-105.0%).

For products such as tablets, capsules and suppositories where a test for uniformity of single dose preparations is required, a test and limit for content uniformity is required when the API is present in the FPP at less than 5 mg or less than 5% of the weight of the dosage unit. Otherwise, the test for mass uniformity may be applied.

Skip testing is acceptable for parameters such as identification of coloring materials and microbial limits, when justified by the submission of acceptable supportive results for five

production batches. When skip testing justification has been accepted, the specifications should include a footnote, stating at minimum the following skip testing requirements: at minimum, every tenth batch and at least one batch annually is tested. In addition, for stability-indicating parameters such as microbial limits, testing will be performed at release and shelf-life during stability studies.

Any differences between release and shelf-life tests and acceptance criteria should be clearly indicated and justified. Note that such differences for parameters, such as dissolution, are normally not accepted. [Reference: ICH Guidelines Q3B, Q3C, Q6A; official monograph]

3.2.P.5.2 Analytical procedures (name, dosage form)

Copies of the in-house analytical procedures used during pharmaceutical development (if used to generate testing results provided in the PD) as well as those proposed for routine testing should be provided. Unless modified, it is not necessary to provide copies of officially recognized compendial analytical procedures.

Tables for summarizing a number of the different analytical procedures and validation information (e.g., HPLC assay/impurity methods) can be found in the 2.3.R Regional information section of the QOS-PD (i.e., *2.3.R.2)*. These tables should be used to summarize the analytical procedures used for determination of the assay, related substances and dissolution of the FPP.

Refer to Section 3.2.S.4.2 of this Guideline for additional guidance on analytical procedures.

3.2.P.5.3 Validation of analytical procedures (name, dosage form)

Analytical validation information, including experimental data, for the analytical procedures used for testing the FPP, should be provided.

Copies of the validation reports for the in-house analytical procedures used during pharmaceutical development (if used to support testing results provided in the PD) as well as those proposed for routine testing should be provided.

Tables for summarizing a number of the different analytical procedures and validation information (e.g., HPLC assay/impurity methods, GC methods) can be found in the 2.3.R Regional information section of the QOS-PD (i.e., *2.3.R.2)*.These tables should be used to summarize the validation information of the analytical procedures used for determination of the assay, related substances, and dissolution of the FPP.

As recognized by regulatory authorities and pharmacopoeias themselves, verification of compendial methods can be necessary. The compendial methods, as published, are typically validated based on an API or an FPP originating from a specific manufacturer. Different sources of the same API or FPP can contain impurities and/or degradation

products or excipients that were not considered during the development of the monograph. Therefore, the monograph and compendial method(s) should be demonstrated suitable for the control of the proposed FPP.

For officially recognized compendial FPP *assay* methods, verification should include a demonstration of specificity, accuracy, and repeatability (method precision).If an officially recognized compendial method is used to control related substances that are not specified in the monograph, full validation of the method is expected with respect to those related substances.

If an officially recognized compendial standard is claimed and an in-house method is used in lieu of the compendial method (e.g., for assay or for related compounds), equivalency of the in-house and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For related compound methods, the sample analyzed should be the placebo spiked with related compounds at concentrations equivalent to their specification limits.
[Reference: ICH Q2]

3.2.P.5.4 Batch analyses (name, dosage form)

Information should include strength and batch number, batch size, date and site of production and use (e.g., used in comparative bioavailability or biowaiver studies, preclinical and clinical studies (if relevant), stability, pilot, scale-up and, if available, production-scale batches) on relevant FPP batches used to establish the specification(s) and evaluate consistency in manufacturing.

Analytical results tested by the company responsible for the batch release of the FPP (generally, the applicant or the FPP manufacturer, if different from the applicant) should be provided for not less than two batches of at least pilot-scale, or in the case of an uncomplicated[1] FPP (e.g., immediate-release solid FPPs (with noted exceptions), non-sterile solutions), not less than one batch of at least pilot-scale and a second batch which may be smaller (e.g., for solid oral dosage forms, 25,000 or 50,000 tablets or capsules) of each proposed strength of the FPP. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

The testing results should include the batch(s) used in the comparative bioavailability or biowaiver studies. Copies of the certificates of analysis for these batches should be provided in the PD and the company responsible for generating the testing results should be identified.

[1]The term "complicated FPP" includes sterile products, metered dose inhaler products, dry powder inhaler products, andtransdermal delivery systems. Other specific products under "complicated FPP" include API containing such as ritonavir/lopinavir FDC tablets and FDCs containing rifampicin or artemisinin. This can be determined on case by case as evidenced from the property of the API and, thus, the applicant is advised to consult the Authority.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "all tests meet specifications." This should include ranges of analytical results, where relevant. For quantitative tests (e.g., individual and total impurity tests and assay tests), it should be ensured that actual *numerical results* are provided rather than vague statements such as "within limits" or "conforms" (e.g., "levels of degradation product A ranged from 0.2 to 0.4 %"). Dissolution results should be expressed at minimum as both the average and range of individual results.

Recommendations for conducting and assessing comparative dissolution profiles can be found in Appendix 3.

A discussion and justification should be provided for any incomplete analyses (e.g., results not tested according to the proposed specification). [Reference: ICH Guidelines Q3B, Q3C, Q6A; official monograph]

3.2.P.5.5 Characterization of impurities (name, dosage form)

A discussion should be provided of all impurities that are potential degradation products (including those among the impurities identified in 3.2.S.3.2 as well as potential degradation products resulting from interaction of the API with other APIs (FDCs), excipients, or the container closure system) and FPP process-related impurities (e.g., residual solvents in the manufacturing process for the FPP). [Reference: ICH Guidelines Q3B, Q3C, Q6A]

3.2.P.5.6 Justification of specification(s) (name, dosage form)

A discussion should be provided on the omission or inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, differences from the officially recognized compendial standard(s), etc. If the officially recognized compendial methods have been modified or replaced, a discussion should be included.

The justification for certain tests, analytical procedures, and acceptance criteria (e.g., degradation products, dissolution method development) may have been discussed in other sections of the PD and does not need to be repeated here, although a cross-reference to its location should be provided.

ICH Guideline Q6A should be consulted for the development of specifications for FPPs.

3.2.P.6 Reference standards or materials (name, dosage form)

Information on the reference standards or reference materials used for testing of the FPP should be provided, if not previously provided in "3.2.S.5 Reference Standards or Materials."

See Section 3.2.S.5 for information that should be provided on reference standards or materials. Information should be provided on reference materials of FPP degradation

products, where not included in 3.2.S.5.[Reference: ICH Guideline Q6A; WHO Technical Report Series, No. 943, Annex 3]

3.2.P.7 Container Closure System (name, dosage form)

A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information (e.g. protection from light, moisture etc.) should be provided. Suitability information should be located in 3.2.P.2.

The WHO *Guidelines on packaging for pharmaceutical products* (WHO Technical Report Series, No. 902, Annex 9, 2002) and the officially recognized pharmacopoeias should be consulted for recommendations on the packaging information for FPPs.

Descriptions, materials of construction and specifications (of the company responsible for packaging the FPP, generally the FPP manufacturer) should be provided for the packaging components that are:

- in direct contact with the dosage form (e.g., container, closure, liner, desiccant, filler);
- used for drug delivery (including the device(s) for multi-dose solutions, emulsions, suspensions, and powders/granules for such);
- used as a protective barrier to help ensure stability or sterility; and,
- necessary to ensure FPP quality during storage and shipping.

Primary packaging components are those that are in direct contact with the API or FPP. The specifications for the primary packaging components should include a specific test for identification (e.g., IR).Specifications for film and foil materials should include limits for thickness or area weight.

Information to establish the suitability (e.g., qualification) of the container closure system should be discussed in Section 3.2.P.2. Comparative studies may be warranted for certain changes in packaging components (e.g., comparative delivery study (droplet size) for a change in manufacturer of dropper tips).

3.2.P.8 Stability (Name, Dosage Form)

3.2.P.8.1 Stability summary and conclusions (name, dosage form)

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life.
The WHO Guidelines on Stability testing of active pharmaceutical ingredients and finished pharmaceutical products (WHO Technical Report Series, No. 1010, 2018, Annex 10) should be consulted for recommendations on the core stability data package.

The purpose of stability testing is to provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability programme also includes the study of product -related factors that influence its quality, for example, interaction of API with excipients, container-closure systems and packaging materials.
Stress testing
Photostability testing should be conducted on at least one primary batch of the FPP, if appropriate. If "protect from light" is stated in one of the officially recognized pharmacopoeias for the API or FPP, it is sufficient to state "protect from light" on labeling, in lieu of photostability studies, when the container closure system is shown to be light protective. Additional stress testing of specific types of dosage forms may be appropriate (e.g., cyclic studies for semi-solid products, freeze-thaw studies for liquid products).
Accelerated, intermediate (if necessary) and long-term testing
Stability data must demonstrate stability of the medicinal product throughout its intended shelf-life under the climatic conditions of Ethiopia. Refer to WHO Technical Report Series, No. 1010, Annex 10, for information on climatic zones.
The required long-term storage conditions for Ethiopia is 30ºC±2ºC/65%±5%RH.The minimum long-term storage condition should thus fulfill the storage conditions of 30ºC±2ºC/65%±5%RH, while the more universal condition of 30ºC±2ºC/75%±5%RH, as recommended by WHO, can also be acceptable. The use of alternative long-term conditions will need to be justified and should be supported with appropriate evidence.

Other storage conditions are outlined in the WHO stability guideline for FPPs packaged in impermeable and semi-permeable containers and those intended for storage in a refrigerator and in a freezer. FPPs intended for storage below -20°C should be treated on a case-by-case basis.
Specification:
Stability studies should include testing of stability-indicating attributes of the FPP, i.e. those that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes, preservative content (e.g. antioxidant or antimicrobial preservatives) and functionality tests (e.g. for a dose delivery system). Examples of testing parameters in the stability studies are listed WHO Technical Report Series, No. 1010, 2018, Annex 10, Appendix 1. Analytical procedures should be fully validated and stability-indicating.

The minimum data required at the time of submission of the dossier (in general):

Type	Storage conduction	Minimum time (months)
Long-term[a]	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	12(for new API) or 6 (for existing API)
Intermediate[b]	30 °C ± 2 °C/65% RH ± 5% RH	6
Accelerated	40°C ±2 °C /75±5%RH	6

[a]*Whether long-term stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ±5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is determined by the climatic zone in which the FPP is intended to be marketed. Testing at a more severe long-term condition can be an alternative to storage at 25 °C/60% RH or 30 °C/65% RH.*

[b]*If 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is the long-term condition, there is no intermediate condition.*

FPP packed in impermeable container

Sensitivity to moisture or potential for solvent loss is not a concern for FPPs packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient RH condition.

FPPs packaged in semi-permeable containers

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological and microbiological stability. This evaluation can be carried out under conditions of low RH, as discussed below.

Type	Storage conduction	Minimum time (months)
Long-term[a]	25 °C ± 2 °C/40% RH ± 5% RH or 30 °C ± 2 °C/35% RH ± 5% RH or	12(for new API) or 6 (for existing API)
Intermediate [b]	30 °C ± 2 °C/35% RH ± 5% RH	6
Accelerated	40°C ±2 °C /not more than (NMT) 25% RH	6

[a]*Whether long-term stability studies are performed at 25 °C ± 2 °C/40% RH ± 5% RH or 30 °C ± 2 °C/35% RH ± 5% RH is determined by the climatic condition under which the FPP is intended to be marketed. Testing at 30 °C/35% RH can be an alternative to the storage condition at 25 °C/40% RH.*

[b]*If 30 °C ± 2 °C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition.*

FPPs intended for storage in a refrigerator

Type	Storage conduction	Minimum time (months)

Long-term	5°C±3 °C	12(for new API) or 6 (for existing API)
Accelerated[a]	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	6

[a]*Whether accelerated stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe accelerated condition can be an alternative to the storage condition at 25 °C/60% RH or 30 °C/65% RH.*[Applicant may consult WHO Technical Series Report No. 1010, 2018, Annex 10. For detail requirement of stability study on finished pharmaceutical product]

To establish the shelf-life, data should be provided on not less than two batches of at least pilot-scale, or in the case of an uncomplicated FPP (e.g., immediate-release solid FPPs (with noted exceptions), non-sterile solutions), not less than one batch of at least pilot-scale and a second batch which may be smaller (e.g., for solid oral dosage forms, 25,000 or 50,000 tablets or capsules) of each proposed strength of the FPP. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

The stability testing program should be summarized, and the results of stability testing should be reported in the dossier and summarized in the tables in the DOS-PD. Bracketing and matrixing of proportional strengths can be applied, if scientifically justified.

For sterile products, sterility should be reported at the beginning and end of shelf-life, and sub-visible particulate matter should be reported frequently, but not necessarily at every test interval. Bacterial endotoxins need only be reported at the initial test interval. Weight loss from plastic containers should be reported over the shelf-life. In-use periods after first opening of the container closure (e.g., parenteral and ophthalmic products) should be justified with experimental data.

Any in-use period and associated storage conditions should be justified with experimental data, for example after opening, reconstitution and/or dilution of any sterile and/or multidose products or after first opening of FPPs packed in bulk multidose containers (e.g. bottles of 1000s). If applicable, the in-use period and storage conditions should be stated in the product information.

The information on the stability studies should include details such as

- storage conditions;
- strength;
- batch number, including the API batch number(s) and manufacturer(s);
- batch size;
- container closure system, including orientation (e.g., erect, inverted, on-side), where applicable; and,
- completed (and proposed) test intervals.

The discussion of test results should focus on observations noted for the various tests, rather than reporting comments such as "all tests meet specifications." This should include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms." Dissolution results should be expressed at minimum as both the average and range of individual results.

Applicants should consult the ICH Q1E guidance document for details on the evaluation and extrapolation of results from stability data (e.g., if significant change was not observed within six months at accelerated condition and the data show little or no variability, the proposed shelf-life could be up to two times the period covered by the long-term data, but should not exceed the long-term data by 12 months).
If long-term studies are conducted at 25 °C ± 2 °C/60% RH ± 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. In this case the initial application should include a minimum of six months' data from a 12-month study at the intermediate storage condition.
In general, "significant change" for an FPP is defined as:

- a change from the initial content of API(s) of 5% or more detected by assay, or failure to meet the acceptance criteria for potency when using biological or immunological procedures;
- any degradation product exceeding its acceptance criterion;
- failure to meet the acceptance criteria for appearance, physical attributes and functionality test (e.g. colour, phase separation, resuspendability, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g. softening of suppositories, melting of creams, partial loss of adhesion for transdermal products) may be expected under accelerated conditions. Also, as appropriate for the dosage form:
- failure to meet the acceptance criterion for pH; or
- failure to meet the acceptance criteria for dissolution for 12 dosage units.

Proposed storage statement and shelf-life

The proposed storage statement and shelf-life (and in-use storage conditions and in-use period, if applicable) for the FPP should be provided.[Reference: WHO TRS No. 1010, Annex 10, Appendix 2; ICH Guidelines Q1A, Q1B, Q1C, Q1D, Q1E, Q3B, Q6A]

3.2.P.8.2 Post-approval stability protocol and stability commitment (name, dosage form)

Primary stability study commitment

When available long-term stability data on primary batches do not cover the proposed shelf-life granted at the time of assessment of the PD, a commitment should be made to continue the stability studies in order to firmly establish the shelf-life. A written

commitment (signed and dated) to continue long-term testing over the shelf-life period should be included in the dossier.

Commitment stability studies

The long-term stability studies for the *commitment batches* should be conducted through the proposed shelf-life on at least three production batches of each strength in each container closure system. Where stability data was not provided for three production batches of each strength, a written commitment (signed and dated) should be included in the dossier.

Ongoing stability studies

An *ongoing stability program* is established to monitor the product over its shelf-life and to determine that the product remains and can be expected to remain within specifications under the storage conditions on the label. Unless otherwise justified, at least one batch per year of product manufactured in every strength and in every container closure system, if relevant, should be included in the stability program (unless none is produced during that year).Bracketing and matrixing may be applicable. A written commitment (signed and dated) to this effect should be included in the dossier.

Any differences in the stability protocols used for the primary batches and those proposed for the *commitment batches* or *ongoing batches* should be scientifically justified.

3.2.P.8.3 Stability data (name, dosage form)

Results of the stability studies should be presented in an appropriate format (e.g., tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be indicated.

The actual stability results/reports used to support the proposed shelf-life should be provided in the PD. For quantitative tests (e.g., individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms.” Dissolution results should be expressed, at minimum, as both the average and range of individual results.

The tabulated summary needs to be approved by the authorized person in the manufacturing site where the data generated. Or where the data is generated by software, the declaration statement that include the date in which the report is produced,and that data is acceptable with authorized signature.

3.2.A Appendices

3.2.A.1 Facilities and Equipment

Not applicable except for biotech products.

3.2.A.2 Adventitious Agents Safety Evaluation

3.2.A.3 Novel Excipients

Provide details of safety (refer to Module 4) and clinical documentation (refer to Module 5) for excipients used for the first time and not used in similar SRA-approved products.

3.2.R Regional Information

3.2.R.1 Production Documentation

3.2.R.1.1 Executed production documents

A minimum of two batches of at least pilot-scale, or in the case of an uncomplicated FPP (e.g., immediate-release solid FPPs (with noted exceptions), non-sterile solutions), not less than one batch of at least pilot-scale (the batch used in comparative bioavailability or biowaiver studies) and a second batch which may be smaller (e.g., for solid oral dosage forms, 25,000 or 50,000 tablets or capsules), should be manufactured for each strength at the time of submission. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

Any difference between the manufacturing process of future production and pivotal batches need discussed and justified.

For solid oral dosage forms, *pilot-scale* is generally, at a minimum, one-tenth that of full production-scale or 100,000 tablets or capsules, whichever is larger.

Copies of the executed production documents should be provided for the batches used in the comparative bioavailability or biowaiver or clinical studies. Any notations made by operators on the executed production documents should be clearly legible.

If not included in the executed batch records through sufficient in-process testing, data should be provided for the batch used in comparative bioavailability, clinical study, or biowaiver studies that demonstrates the uniformity of this batch. The data to establish the uniformity of the biobatch should involve testing to an extent greater than that required in routine quality control.

English translations of executed records should be provided, where relevant.

3.2.R.1.2 Master production documents

Copies of the FPP master production documents (blank batch manufacturing document) should be provided for each proposed strength, commercial batch size, and manufacturing site.

The details in the master production documents should include, but not be limited to, the following:

a) master formula;

b) dispensing, processing, and packaging sections with relevant material and operational details;
c) relevant calculations (e.g., if the amount of API is adjusted based on the assay results or on the anhydrous basis);
d) identification of all equipment by, at minimum, type and working capacity (including make, model, and equipment number, where possible);
e) process parameters (e.g., mixing time, mixing speed, milling screen size, processing temperature range, granulation end-point, tablet machine speed (expressed as target and range));
f) list of in-process tests (e.g., appearance, pH, assay, blend uniformity, viscosity, particle size distribution, LOD, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity, filter integrity checks) and specifications;
g) sampling plan with regard to the:
    i. steps where sampling should be done (e.g., drying, lubrication, compression),
    ii. number of samples that should be tested (e.g., for blend uniformity testing of low dose FPPs, blend drawn using a sampling thief from x positions in the blender), and,
    iii. frequency of testing (e.g., weight variation every x minutes during compression or capsule filling);
h) precautions necessary to ensure product quality (e.g., temperature and humidity control, maximum holding times);
i) for sterile products, reference to standard operating procedures (SOP) in appropriate sections and a list of all relevant SOPs at the end of the document;
j) theoretical and actual yield; and,
k) compliance statement with the GMP requirements (refer to documents in Module 1).

[Reference: WHO Technical Report Series, Nos. 902 and No. 908]

3.2.R.2 Analytical Procedures and Validation Information

The tables presented in section 2.3.R.2 in the DOS-PD template should be used to summarize the analytical procedures and validation information from sections 3.2.S.4.2, 3.2.S.4.3, 2.3.S.4.4 (c), 2.3.S.7.3 (b), 3.2.P.5.2 and 3.2.P.5.3, where relevant.

MODULE 4: NON-CLINICAL STUDY REPORTS

The application of this module will depend on the molecule under consideration. For new molecule (Innovator), full data on non-clinical study reports will be required while for those molecules which are not innovator (new) molecule but new to the Ethiopian market literature review on non-clinical study will be required. This section of the Guideline is not required for generic products in which a molecule (s) of FPP is registered in Ethiopia. In such cases, reference to the list suffices.

4.1 Table of Contents of Module 4

A Table of Contents should be provided that lists all of the nonclinical study reports and gives the location of each study report in the PD.

4.2 Study Reports

The study reports should be presented in the following order:

4.2.1 Pharmacology
- 4.2.1.1 Primary Pharmacodynamics
- 4.2.1.2 Secondary Pharmacodynamics
- 4.2.1.3 Safety Pharmacology
- 4.2.1.4 Pharmacodynamic Drug Interactions

4.2.2 Pharmacokinetics
- 4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)
- 4.2.2.2 Absorption
- 4.2.2.3 Distribution
- 4.2.2.4 Metabolism
- 4 2.2.5 Excretion
- 4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)
- 4.2.2.7 Other Pharmacokinetic Studies

4.2.3 Toxicology
- 4.2.3.1 Single-Dose Toxicity (in order by species, by route)
- 4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)
- 4.2.3.3 Genotoxicity
- 4.2.3.3.1 In vitro
- 4.2.3.3.2 In vivo (including supportive toxico-kinetics evaluations)
- 4.2.3.4 Carcinogenicity (including supportive toxico-kinetics evaluations)
- 4.2.3.4.1 Long-term studies (in order by species, including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- 4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- 4.2.3.4.3 Other studies
- 4.2.3.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxico-kinetics evaluations) [If modified study designs are used, the following sub-headings should be modified accordingly.]

4.2.3.5.1 Fertility and early embryonic development
4.2.3.5.2 Embryo-fetal development
4.2.3.5.3 Prenatal and postnatal development, including maternal function
4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
4.2.3.6 Local Tolerance
4.2.3.7 Other Toxicity Studies (if available)
4.2.3.7.1 Antigenicity
4.2.3.7.2 Immunotoxicity
4.2.3.7.3 Mechanistic studies (if not included elsewhere)
4.2.3.7.4 Dependence
4.2.3.7.5 Metabolites
4.2.3.7.6 Impurities
4.2.3.7.7 Other

4.3 Literature References

MODULE 5: CLINICAL STUDY REPORTS

This section of the Guideline is applicable only for medicines which are new molecules (Innovator product) where the medicine is not yet registered in Ethiopia. For FPPs in which the molecule(s) is new to the Ethiopian market but not innovator product which have a global marketing experience, the applicant should submit literature review on l safety and efficacy data as outline in this Guideline. For multisource generic products having a molecule(s) already registered in Ethiopia and requiring BE study, only section 5.3.3 of Module 5 needs to be supported with actual experimental evidence and where applicable reference to literature can be considered for other section. For generic products requiring clinical equivalence study, in cases where comparative clinical evidence of a pharmacokinetics (PK) BE study cannot be conducted, section 5.3.4 of Module 5 may be required, to be determined on a case-by-case basis.

The information provided below is not intended to indicate what studies are required for successful registration. It indicates an appropriate organization for the clinical study reports that need to be submitted with the application.

The placement of a report should be determined by the primary objective of the study. Each study report should appear in only one section. Where there are multiple objectives, the study should be cross-referenced in the various sections. An explanation, such as “not applicable” or “no study conducted,” should be provided when no report or information is available for a section or subsection.

5.1 Table of Contents of Module 5

5.2 Tabular Listing of All Clinical Studies

A tabular listing of all clinical studies and related information should be provided. For each study, this tabular listing should generally include the type of information identified in Table 5.1 of this Guideline. Other information can be included in this table if the applicant considers it useful. The sequence in which the studies are listed should follow the sequence described in Section 5.3 below. Use of a different sequence should be noted and explained in an introduction to the tabular listing.

5.3 Clinical Study Reports

5.3.1 Reports of Biopharmaceutic Studies

BA studies evaluate the rate and extent of release of the active substance from the medicinal product. Comparative BA or BE studies may use PK, PD, clinical, or in vitro dissolution endpoints, and may be either single dose or multiple dose. When the primary purpose of a study is to assess the PK of a drug, but also includes BA information, the study report should be submitted in Section 5.3.1, and referenced in Sections 5.3.1.1 and/or 5.3.1.2.

5.3.1.1 Bioavailability (BA) study reports

BA studies in this section should include:

- studies comparing the release and systemic availability of a drug substance from a solid oral dosage form to the systemic availability of the drug substance given intravenously or as an oral liquid dosage form;
- dosage form proportionality studies; and,
- food-effect studies.

Reference to literature suffices for generic products.

5.3.1.2 Comparative BA and BE study reports

Studies in this section compare the rate and extent of release of the drug substance from similar drug products (e.g., tablet to tablet, tablet to capsule). Comparative BA or BE studies may include comparisons between

- the drug product used in clinical studies supporting effectiveness and the to-be-marketed drug product, the drug product used in clinical studies supporting effectiveness, and the drug product used in stability batches; and,
- similar drug products from different manufacturers.

5.3.1.3 In vitro–in vivo correlation study reports

In vitro dissolution studies that provide BA information, including studies used in seeking to correlate in vitro data with in vivo correlations, should be placed in section 5.3.1.3. reports of in vitro dissolution tests used for batch quality control and/or batch release should be placed in the Quality section (module 3) of the PD.

5.3.1.4 Reports of bioanalytical and analytical methods for human studies

Bioanalytical and/or analytical methods for biopharmaceutic studies or in vitro dissolution studies should ordinarily be provided in individual study reports. Where a method is used in multiple studies, the method and its validation should be included once in section 5.3.1.4 and referenced in the appropriate individual study reports.

5.3.2 Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials

Human biomaterials is a term used to refer to proteins, cells, tissues, and related materials derived from human sources that are used in vitro or ex vivo to assess PK properties of drug substances. Examples include cultured human colonic cells that are used to assess permeability through biological membranes and transport processes, and human albumin that is used to assess plasma protein binding. Of particular importance is the use of human biomaterials such as hepatocytes and/or hepatic microsomes to study metabolic pathways and to assess drug-drug interactions with these pathways. Studies using biomaterials to address other properties (e.g., sterility or pharmacodynamics) should not be placed in the Clinical Study Reports Section, but in the Nonclinical Study Section (Module 4).

For generic products and if the APIs with the stated dosage form registered in Ethiopia, cross-reference to relevant literature suffices.

5.3.2.1 Plasma protein binding study reports

Ex vivo protein binding study reports should be provided here. Protein binding data from PK blood and/or plasma studies should be provided in section 5.3.3.

5.3.2.2 Reports of hepatic metabolism and drug interaction studies

Reports of hepatic metabolism and metabolic drug interaction studies with hepatic tissue should be placed here.

5.3.2.3 Reports of studies using other human biomaterials

Reports of studies with other biomaterials should be placed in this section.

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

Assessment of the PK of a drug in healthy subjects and/or patients is considered critical to designing dosing strategies and titration steps, to anticipating the effects of concomitant drug use, and to interpreting observed pharmacodynamic differences. These assessments should provide a description of the body's handling of a drug over time, focusing on maximum plasma concentrations (peak exposure), area-under-curve (total exposure), clearance, and accumulation of the parent drug and its metabolite(s), in particular, those that have pharmacological activity. The PK studies whose reports should be included in sections 5.3.3.1 and 5.3.3.2 are generally designed to: (1) measure plasma drug and metabolite concentrations over time; (2) measure drug and metabolite concentrations in urine or feces, when useful or necessary; and/or, (3) measure drug and metabolite binding to protein or red blood cells. On occasion, PK studies may include measurement of drug distribution into other body tissues, body organs, or fluids (e.g., synovial fluid or cerebrospinal fluid), and the results of these tissue distribution studies should be included in section 5.3.3.1 to 5.3.3.2, as appropriate. These studies should characterize the drug's PK and provide information about the absorption, distribution, metabolism, and excretion of a drug and any active metabolites in healthy subjects and/or patients. Studies of mass balance and changes in PK related to dose (e.g., determination of dose proportionality) or time (e.g., due to enzyme induction or formation of antibodies) are of particular interest and should be included in sections 5.3.3.1 and/or 5.3.3.2. Apart from describing mean PK in normal and patient volunteers, PK studies should also describe the range of individual variability. The study of human PK study reports should fulfill the requirements for bioequivalence as described in Annex IV of this Guideline.

5.3.3.1 Healthy subject PK and initial tolerability study reports

Reports of PK and initial tolerability studies in healthy subjects should be placed in this section.

5.3.3.2 Patient PK and initial tolerability study reports

Reports of PK and initial tolerability studies in patients should be placed in this section. Most of the time for generic products, cross-reference to literature suffices. However,

when PK studies are not possible on healthy subjects because of toxicity and other issues, this section should be completed where applicable.

5.3.3.3 Intrinsic factor PK study reports

Reports of PK studies to assess effects of intrinsic factors, should be placed in this section. Reports of PK studies to assess differences in systemic exposure as a result of changes in PK due to intrinsic (e.g., age, gender, racial, weight, height, disease, genetic polymorphism, and organ dysfunction) factors should be placed in this section.

5.3.3.4 Extrinsic factor PK study reports

Reports of PK studies to assess effects of extrinsic factors (e.g., drug-drug interactions, diet, smoking, and alcohol use) factors should be organized in this section.

5.3.3.5 Population PK study reports

Reports of population PK studies based on sparse samples obtained in clinical trials, including efficacy and safety trials, should be placed in this section.

5.3.4 Reports of Human Pharmacodynamic (PhD) Studies

This section of the Guideline does not require experimental evidence for generic products and medicines already registered in Ethiopia. Exceptions are when meaningful PK studies cannot be conducted as a result of difficulties, such as inadequate measurement of the active pharmaceutical substance in biological fluids. See Annex IV for further clarification.

Reports of studies with a primary objective of determining the PhD effects of a drug product in humans should be placed in this section. Reports of studies whose primary objective is to establish efficacy or to accumulate safety data, however, should be placed in section 5.3.5.

This section should include reports of: (1) studies of pharmacologic properties known or thought to be related to the desired clinical effects (biomarkers); (2) short-term studies of the main clinical effect; and, (3) PD studies of other properties not related to the desired clinical effect. Because a quantitative relationship of these pharmacological effects to dose and/or plasma drug and metabolite concentrations is usually of interest, PD information is frequently collected in dose response studies or together with drug concentration information in PK studies (concentration-response or PK/PD studies). Relationships between PK and PD effects that are not obtained in well-controlled studies are often evaluated using an appropriate model and used as a basis for designing further dose-response studies or, in some cases, for interpreting effects of concentration differences in population subsets.

Dose-finding, PD, and/or PK-PD studies can be conducted in healthy subjects and/or patients and can also be incorporated into the studies that evaluate safety and efficacy in a clinical indication. Reports of dose-finding, PD, and/or PK/PD studies conducted in

healthy subjects should be placed in section 5.3.4.1, and the reports for those studies conducted in patients should be placed in section 5.3.4.2.

In some cases, the short-term PD, dose-finding, and/or PK-PD information found in pharmacodynamic studies conducted in patients will provide data that contribute to assessment of efficacy, either because they show an effect on an acceptable surrogate marker (e.g., blood pressure) or on a clinical benefit endpoint (e.g., pain relief). Similarly, a PD study may contain important clinical safety information. When these studies are part of the efficacy or safety demonstration, they are considered clinical efficacy and safety studies that should be included in section 5.3.5, not in section 5.3.4.

5.3.4.1 Healthy subject PD and PK/PD study reports

PD and/or PK/PD studies having non-therapeutic objectives in healthy subjects should be placed in this section.

5.3.4.2 Patient PD and PK/PD study reports

PD and/or PK/PD studies in patients should be submitted in this section.

5.3.5 Reports of Efficacy and Safety Studies

For generic medicines in which the molecule(s) of FPP are registered in Ethiopia cross reference to literature will suffice. This section should include reports of all clinical studies of efficacy and/or safety carried out with the drug, conducted by the sponsor, or otherwise available, including all completed and all ongoing studies of the drug in proposed and non-proposed indications. The study reports should provide the level of detail appropriate to the study and its role in the application.

In cases where the application includes multiple therapeutic indications, the reports should be organized in a separate section 5.3.5 for each indication. In such cases, if a clinical efficacy study is relevant to only one of the indications included in the application, it should be included in the appropriate section 5.3.5; if a clinical efficacy study is relevant to multiple indications, the study report should be included in the most appropriate section 5.3.5 and referenced as necessary in other sections 5.3.5, for example, section 5.3.5A, section 5.3.5B.

5.3.5.1 Study reports of controlled clinical studies pertinent to the claimed indication

The controlled clinical study reports should be sequenced by type of control:

- Placebo control (could include other control groups, such as an active comparator or other doses);
- No-treatment control;
- Dose-response (without placebo);
- Active control (without placebo); or,
- External (historical) control, regardless of the control treatment.

Within each control type, where relevant to the assessment of drug effect, studies should be organized by treatment duration. Studies of indications other than the one proposed in the application, but that provide support for efficacy in the proposed use, should be included in section 5.3.5.1.

Where a pharmacodynamic study contributes to evidence of efficacy, it should be included in section 5.3.5.1. The sequence in which studies were conducted is not considered pertinent to their presentation. Thus, placebo-controlled trials, whether early or late, should be placed in section 5.3.5.1. Controlled safety studies, including studies in conditions that are not the subject of the application, should also be reported in section 5.3.5.1.

5.3.5.2 Study reports of uncontrolled clinical studies

Study reports of uncontrolled clinical studies (e.g., reports of open label safety studies) should be included in section 5.3.5.2. This includes studies in conditions that are not the subject of the marketing application.

5.3.5.3 Reports of analyses of data from more than one study

Examples of reports that would be found in this section include: a report of a formal meta-analysis or extensive exploratory analysis of efficacy to determine an overall estimate of effect size in all patients and/or in specific subpopulations, and a report of an integrated analysis of safety that assesses such factors as the adequacy of the safety database, estimates of event rates, and safety with respect to variables such as dose, demographics, and concomitant medications. A report of a detailed analysis of bridging, considering formal bridging studies, other relevant clinical studies, and other appropriate information (e.g., PK and PD information), should be placed in this section if the analysis is too lengthy for inclusion in the Clinical Summary.

5.3.5.4 Other study reports

This section can include:

- Reports of interim analyses of studies pertinent to the claimed indications;
- Reports of controlled safety studies not reported elsewhere; and,
- Reports of controlled or uncontrolled studies not related to the claimed indication.

5.3.6 Reports of Post-Marketing Experience

For products that are currently marketed, reports that summarize marketing experience (including all significant safety observations) should be included in this section.

5.3.7 Case Report Forms and Individual Patient Listings

Case report forms and individual patient data listings are subject to good clinical practice inspection where applicable.

5.4 Literature References

Copies of referenced documents, including important published articles, official meeting minutes, or other regulatory guidance or advice should be provided here. This includes copies of all references cited in the Clinical Overview, and copies of important references cited in the Clinical Summary or in the individual technical reports that were provided in Module 5. Only one copy of each reference should be provided. Copies of references that are not included here should be immediately available upon request.

ANNEX I: APPLICATION FORM FOR REGISTRATION

Food and Drug Authority of Ethiopia
P.O. Box 5681, Addis Ababa, Ethiopia

A. Type of application (check the box applicable)

New Application	☐
Periodic re-registration	☐
Variation to existing marketing authorization (If selected, complete the information below.)	☐
• Previous registration number	
• Previous registration condition	
• Brief description of change intended	
• Reasons for variations	

B. Details on the product

Proprietary name (trade name)			
Approved generic name (s) (use INN if any)			
Standard claimed (BP, Ph.In, Ph. Eur., USP, IH, etc.)			
Strength(s) per dosage unit			
Dosage form			
Route of administration			
Shelf life (months)			
Storage condition			
Visual description			
Description of container closure			
Packaging and pack size			
Complete qualitative and quantitative composition (indicate per unit dosage form, e.g., per tablet, per 5ml, etc.) **	Composition	Strength	Function
** Add/delete as many rows and columns as needed.			
Complete qualitative and quantitative composition (indicate per batch in Kg, L,	Composition	Strength	Function

etc.). Type of batches should be described.			
Statement of similarity and difference of clinical, bio-batch, stability, validation, and commercial batch sizes			
Regulatory situation in other country (Provide a list of countries in which this product has been granted a marketing authorization and the restrictions on sale or distribution, e.g., withdrawn from the market, etc.)			

C. Details on the applicant

Name	
Business address	
Street number and postal address	
Telephone number	
Fax number	
E-mail and website address	
Contact person in a company	Name:
	Position:
	Postal address:
	Telephone number:
	Fax number:
	E-mail:
Details of Manufacturer, if different from above	<<Insert the required information as indicated above>>>

D. Details on active pharmaceutical(s) ingredient(s) manufacturer

Name of manufacturer	
Street and postal address	
Telephone/Fax number	
E-mail	
Retest period/Shelf life	

E. Details on local agent (representative) in Ethiopia

Name of local agent	
Sub-city and postal address	
Telephone/Fax number	
E-mail	
Contact person in company Address of company	

F. Details on dossiers submitted with the application

Section of dossier	**Annex, page number, etc.**
Module 1	
Module 2	
Module 3	
Module 4	
Module 5	

CERTIFICATION BY A RESPONSIBLE PERSON IN THE APPLICANT COMPANY

I, the undersigned, certify that all the information in the accompanying documentation concerning an application for a marketing authorization for:

Proprietary name (trade name)	
Approved generic name(s) (INN)	
Strength(s) per dosage unit	
Dosage form	
Applicant	
Manufacturer	

… is correct and true and reflects the total information available. I further certify that I have examined the following statements and I attest to their accuracy.

1. The current edition of the WHO Guideline, "Good manufacturing practices for pharmaceutical products," is applied in full in all premises involved in the manufacture of this product.
2. The formulation per dosage form correlates with the master formula and with the batch manufacturing record forms.
3. The manufacturing procedure is exactly as specified in the master formula and batch manufacturing record forms.
4. Each batch of all starting materials is either tested or certified against the full specifications in the accompanying documentation and comply fully with those specifications *before it is released for manufacturing purposes.*
5. All batches of active pharmaceutical ingredient(s) are obtained from the source(s) specified in the accompanying documentation.
6. No batch of active pharmaceutical ingredient will be used unless a copy of the batch certificate established by the active ingredient manufacturer is available.
7. Each batch of the container/closure system is tested or certified against the full specifications in the accompanying documentation and complies fully with those specifications *before it is released for manufacturing purposes.*
8. Each batch of the finished product is either tested or certified against the full specifications in the accompanying documentation and complies fully with the release specifications *before it is released for sale.*
9. The person releasing the product for sale is an authorized person as defined by the WHO guideline "Good manufacturing practices: Authorized person - the role, functions and training."
10. The procedures for control of the finished product have been validated for this formulation.
11. The market authorization holder has a standard operating procedure for handling adverse reaction reports on its products.
12. The market authorization holder has a standard operating procedure for handling batch recalls of its products.

13. All the documentation referred to in this Certificate is available for review during a GMP inspection.
14. Any clinical trials including bioequivalence study were conducted according to WHO's "Guidelines for good clinical practice (GCP) for trials on pharmaceutical products."

Signature_____

Name _____

Position in company (print or type) _____

Date: _____

ANNEX II: CERTIFICATE OF PHARMACEUTICAL PRODUCTS1

This certificate conforms to the format recommended by the World Health Organization
(General instructions and explanatory notes attached)
No. of Certificate _____
Exporting (certifying country): _____
Importing (requesting country): _____
1. Name and dosage form of the product: _____
1.1. Active ingredient(s)[2] and amount(s) per unit dose[3]: _____
For complete composition including excipients, see attached[4]: _____
1.2. Is this product licensed to be placed on the market for use in the exporting country?[5]
yes/no (*Key in as appropriate*)
1.3 Is this product actually on the market in the exporting country? (*Key in as appropriate*)
yes/no/unknown
If the answer to 1.2. is **yes**, continue with section 2A and omit section 2B. If the answer to 1.2 is no, omit section 2A and continue with section 2B:[6]
2.A.1. Number of product license[7] and date of issue:
_____
2.A.2. Product license holder (name and address):
_____
2.A.3. Status of product license holder:[8]
a/b/c *(Key in appropriate category as defined in note 8)*
2.A.3.1. For categories (b) and (c), provide the name and address of the manufacturer producing the dosage form:[9] _____
2.A.4. Is a summary basis for approval appended?[10]
yes/no (*Key in as appropriate*)
2.A.5. Is the attached, officially approved product information complete and consonant with the license?[11]
yes/no/not provided (*Key in as appropriate*)
2.A.6. Applicant for Certificate, if different from license holder (name and address):[12]
_____--
2.B.1. Applicant for Certificate (name and address):
_____
2.B.2. Status of applicant:
a b/c (*Key in appropriate category as defined in footnote 8)*
2.B.2.1. For categories (b) and (c), provide the name and address of the manufacturer producing the dosage form:[9] _____
2.B.3. Why is marketing authorization lacking?
not required/not requested/under consideration/refused (*Key in as appropriate*)

2.B.4. Remarks:[13]

3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced?

If not or not applicable, proceed to question 4.

yes/no/not applicable[14] (*Key in as appropriate*)

3.1. Periodicity of routine inspections (years): _____

3.2. Has the manufacture of this type of dosage form been inspected?

yes/no

3.3. Do the facilities and operations conform to good manufacturing practices (GMP) as recommended by the World Health Organization (WHO)?[15]

yes/no/not applicable[14] (*Key in as appropriate*)

4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product:[16]

yes/no *(Key in as appropriate)*

If no, explain: _____

Address of certifying authority: _____

Telephone: _____

Fax no.:_____

E-mail: _____

Name of authorized person: _____

Signature: _____

Stamp and date: _____

General instructions

Please refer to the Guideline for full instructions on how to complete this form and for information on the implementation of the Scheme.

This form should always be submitted as a hard copy, with responses printed in type rather than handwritten.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

[1] This Certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the Certificate in the exporting country. It is for a single product only, since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.

[2] Use, whenever possible, the International Nonproprietary Names (INNs) or national nonproprietary names.

[3] The formula (complete composition) of the dosage form should be given on the Certificate or should be appended.

[4] Details of quantitative composition are preferred, but their provision is subject to the agreement of the product-license holder.

[5] When applicable, append details of any restriction applied to the sale, distribution, or administration of the product that is specified in the product license.

[6] Sections 2A and 2B are mutually exclusive.

[7] Indicate, when applicable, if the license is provisional, or the product has not yet been approved.

[8] Specify whether the person responsible for placing the product on the market:

(a) manufactures the dosage form;

(b) packages and/or labels a dosage form manufactured by an independent company; or,

(c) is not involved in any of the above.

[9] This information can only be provided with the consent of the product-license holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information.

It should be noted that information concerning the site of production is part of the product license. If the production site is changed, the license has to be updated or it is no longer valid.

[10] This refers to the document, prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed.

[11] This refers to product information approved by the competent national regulatory authority, such as Summary Product Characteristics (SPC).

[12] In this circumstance, permission for issuing the Certificate is required from the product-license holder. This permission has to be provided to the Authority by the applicant.

[13] Please indicate the reason that the applicant has provided for not requesting registration.

(a) the product has been developed exclusively for the treatment of conditions — particularly tropical diseases — not endemic in the country of export;

(b) the product has been reformulated with a view to improving its stability under tropical conditions;

(c) the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import;

(d) the product has been reformulated to meet a different maximum dosage limit for an active ingredient; or,

(e) any other reason (please specify).

[14] Not applicable means the manufacture is taking place in a country other than that issuing the product Certificate and inspection is conducted under the aegis of the country of manufacture.

[15] The requirements for good practices in the manufacture and quality control of drugs referred to in the Certificate are those included in the Thirty-second Report of the Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series No. 823, 1992, Annex 1. Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No. 822, 1992, Annex 1).

[16] This section is to be completed when the product-license holder or applicant conforms to status (b) or (c), as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances, the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.

ANNEX III: SUMMARY OF PRODUCT CHARACTERISTICS

(With proposed sentence patterns and illustrative examples)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT
   {(Invented) name of product <strength><pharmaceutical form>}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

For excipients, see 6.1.

This include the quantitative composition of special excipients (such as Lactose, Aspartame, Preservative and Antioxidants)

3. PHARMACEUTICAL FORM

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

<This pharmaceutical product is for diagnostic use only. >

4.2. Posology and method of administration [*See example below*.]

Adults

Children and adolescents (4 to 17 years of age)

General administration recommendations

Special dosing considerations in adults

4.3. Contraindications

<Hypersensitivity to the API(s) or to any of the excipients <or {residues}>

4.4. Special warnings and special precautions for use [*See example below*.]

Drug interactions

Acute hemolytic

Hyperglycemia

Patients with coexisting conditions

4.5. Interaction with other FPPs and other forms of interaction [*See example below*.]

Rifabutin)

Ketoconazole)

Itraconazole)

Nevirapine)

HMG -CoA reductase inhibitors)

Rifampicin)

4.6. Pregnancy and lactation [*See example below*.]

Use during pregnancy)

Use during lactation)

4.7. Effects on ability to drive and use machines

< {Invented name} has <no or negligible influence><minor or moderate influence><major influence> on the ability to drive and use machines.> [describe effects where applicable]

<No studies on the effects on the ability to drive and use machines have been performed.><Not relevant.>

4.8. Undesirable effects [*See example below*.]

Laboratory test findings)

Post-marketing experience)

4.9. Overdose

<No case of overdose has been reported.>

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: {group}

ATC code: {code}

Mechanism of action

Microbiology (when applicable)

Drug resistance (when applicable)

Cross resistance (when applicable)

Pharmacodynamic effects

Adults

Pediatric patients

5.2. Pharmacokinetic properties

Absorption

Distribution

Biotransformation

Elimination

Characteristics in patients

5.3. Preclinical safety data

<Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.><Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.>

<Adverse reactions not observed in clinical studies but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows.>

Mutagenicity

Carcinogenicity

Developmental Toxicity

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients [*See example below*.]

Capsule content)

Capsule shell)

Printing ink)

6.2. Incompatibilities

<Not applicable.>

<In the absence of compatibility studies, this pharmaceutical product must not be mixed with other pharmaceutical products.>

<This pharmaceutical product must not be mixed with other pharmaceutical products except those mentioned in 6.6.>

6.3. Shelf life

<...><6 months><...><1 year><18 months><2 years><30 months><3 years><...>

6.4. Special precautions for storage

<Do not store above <25°C> 30°C»

<Store at 2°C - 8°C (in a refrigerator» <Store in a freezer>

<Do not <refrigerate><or><freeze»

<Store in the original <package><container» <Keep the container tightly closed>

<Keep the container in the outer carton>

<No special precautions for storage>

<in order to protect from <light><moisture»

6.5. Nature and contents of container

<Not all pack sizes may be marketed.>

6.6. Instructions for use and handling <and disposal>

<No special requirements.>

7. MARKETING AUTHORISATION HOLDER
8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS
9. DATE OF FIRST AUTHORISATION/RENEWALOF THE AUTHORISATION
10. DATE OF REVISION OF THE TEXT

ANNEX IV: REQUIREMENTS FOR BIOEQUIVALENCE STUDY

Reports of Human PK studies (Bioequivalence or BE report) is required for those oral dosage forms of drugs which are known to pose a bioavailability problem. The test study should be compared with the innovator (comparator) or leading registered medicine with the Authority.

Assessment of PK equivalence will normally require an in vivo study, or justification that such a study should not be required in a particular case. An in-vitro test can be used if the product is in the same solid dosage form but in a different strength and is proportionally similar in its active and inactive ingredients as another product made by the same manufacturer and of known bioavailability.

In vivo bioequivalence studies are preferred where a drug produces meaningful concentrations in accessible biologic fluid, such as plasma. Where a drug does not produce measurable concentrations in accessible biologic fluid, comparative clinical trials or pharmacodynamics studies may be necessary and should be documented as discussed in this section of the guideline.

Applicant need to consult WHO Technical Report Series No. 992, 2015 Annex 7 in connection with the conduct of equivalence studies i.e. requirements for Pharmacokinetic comparative bioavailability (bioequivalence) studies in human, Pharmacodynamic equivalence studies, Clinical equivalence studies and in vitro equivalence studies).

1. When equivalence studies are not necessary

The following types of multisource pharmaceutical products are considered to be equivalent without need of further documentation:

a) when the pharmaceutical product is to be administered parenterally (e.g., intravenously, subcutaneously, or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations as in the comparator product. Certain excipients(e.g., buffer, preservative, and antioxidant) may be different, provided it can be shown that the change(s) in these excipients would not affect the safety and/or efficacy of the pharmaceutical product; The same principles are applicable for parenteral oily solutions but, in this case, the use of the same oily vehicle is essential. Similarly, for micellar solutions, solutions containing complexing agents or solutions containing co-solvents of the same qualitative and quantitative composition of the functional excipients are necessary in order to waive equivalence studies and the change of other excipients should be critically reviewed;

b) when pharmaceutically equivalent products are solutions for oral use (e.g., syrups, elixirs, and tinctures), contain the API in the same molar concentration as the comparator product, and contain essentially the same excipients in similar concentrations. Excipient(s) known to affect gastrointestinal (GI) transit, GI permeability, and, hence, absorption or stability of the API in the GI tract, should be critically reviewed;

c) when pharmaceutically equivalent products are in the form of powders for reconstitution as a solution and the resultant solution meets either criterion (a) or criterion (b) above;
d) when pharmaceutically equivalent products are gases;
e) when pharmaceutically equivalent products are otic or ophthalmic products prepared as aqueous solutions and contain the same API(s)in the same molar concentration and essentially the same excipients in similar concentrations. Certain excipients (e.g., preservative, buffer, substance to adjust tonicity, or thickening agent) may be different provided their use is not expected to affect bioavailability, safety and/or efficacy of the product;
f) when pharmaceutically equivalent products are topical products prepared as aqueous solutions and contain the same API(s) in the same molar concentration and essentially the same excipients in comparable concentration; or,
g) when pharmaceutically equivalent products are aqueous solutions for nebulizer inhalation products or nasal sprays, intended to be administered with essentially the same device, and contain the same API(s) in the same concentration and essentially the same excipients in similar concentrations. The pharmaceutical product may include different excipients provided their use is not expected to affect bioavailability, safety and/or efficacy of the product.

For situations (b), (c), (e), (f), and (g) above, it is incumbent upon the applicant to demonstrate that the excipients in the pharmaceutically equivalent product are essentially the same and in concentrations comparable to those in the comparator product or, where applicable (i.e., (e) and (g)), that their use is not expected to affect the safety and/or efficacy of the product. In the event that this information cannot be provided by the applicant and the Authority does not have access to the relevant data, it is incumbent upon the applicant to perform appropriate studies to demonstrate that differences in excipients or devices do not affect product performance.

2. When in vivo equivalence studies are necessary

Except for the cases discussed above (section 1), equivalence of the product to be marketed should be determined with the comparator product as described in this section of the Guideline and the report should be provided in Module 5 of the PD.

3. In vivo studies

For certain medicines and dosage forms, in vivo documentation of equivalence, through either a pharmacokinetic bioequivalence study, a comparative pharmacodynamic study, or a comparative clinical trial, is regarded as especially important. In vivo documentation of equivalence is needed when there is a risk that possible differences in bioavailability may result in therapeutic inequivalence. Examples are listed below:

a) Oral immediate-release pharmaceutical products with systemic action, except for the conditions outlined in section 8 below.

b) Non-oral, non-parenteral pharmaceutical products designed to act systemically (such as transdermal patches, suppositories, nicotine chewing gum, testosterone gel and skin-inserted contraceptives);
c) Modified-release pharmaceutical products designed to act systemically, except for the conditions outlined in section 8 below;
d) Fixed-dose combination (FDC) products with systemic action, where at least one of the APIs requires an in vivo study; or,
e) Non-solution pharmaceutical products, which are for non-systemic use (e.g., for oral, nasal, ocular, dermal, rectal or vaginal application) and are intended to act without systemic absorption. In these cases, the equivalence is established through, e.g., comparative clinical or pharmacodynamic, local availability studies, and/or in vitro studies. In certain cases, measurement of the concentration of the API may still be required for safety reasons, i.e., in order to assess unintended systemic absorption.

4. In vitro studies

For certain APIs and dosage forms, in vitro documentation of equivalence may be appropriate. In vitro approaches for systemically-acting oral products are described in section 8 below.

5. In vivo equivalence studies in humans

5.1. General considerations

Pharmacokinetic, pharmacodynamic and clinical studies are all clinical trials and should therefore be carried out in accordance with the provisions and prerequisites for a clinical trial, as outlined in the current Guidelines for good clinical practice (GCP) for trials on pharmaceutical products.

5.2. Study protocol

A bioequivalence study should be carried out in accordance with a protocol agreed upon and signed by the investigator and the sponsor. The protocol and its attachments and/or appendices should state the aim of the study and the procedures to be used, the reasons for proposing the study to be undertaken in humans, the nature and degree of any known risks, assessment methodology, criteria for acceptance of bioequivalence, the groups from which it is proposed that trial subjects be selected, and the means for ensuring that they are adequately informed before they give their consent. The investigator is responsible for ensuring that the protocol is strictly followed. Any change(s) required must be agreed upon and signed by the investigator and sponsor, and appended as amendments, except when necessary to eliminate an apparent immediate hazard or danger to a trial subject.

A signed and dated study protocol, together with the study report, should be presented to the Authority as Module 5 of the PD in order to obtain the marketing authorization for the multisource product.

5.3. Study design

Bioequivalence studies are designed to compare the in vivo performance of a multisource product with that of a comparator product. Such studies on products designed to deliver the API for systemic exposure serve two purposes:

- as a surrogate for clinical evidence of the safety and efficacy of the multisource product;
- as an in vivo measure of pharmaceutical quality.

The design of the study should maximize the sensitivity to detect any difference between products, minimize the variability that is not caused by formulation effects and eliminate bias as far as possible. Test conditions should reduce variability within and between subjects.

In general, for a bioequivalence study involving a multisource product and a comparator product, a randomized, two-period, two-sequence, single-dose, cross-over study conducted with healthy volunteers is the preferred study design. In this design each subject is given the multisource product and the comparator product in randomized order. An adequate wash-out period should follow the administration of each product. The wash-out period between doses of each formulation should be long enough to permit the elimination of essentially the entire previous dose from the body. The wash-out period should be the same for all subjects and should normally be more than five times the terminal half-life of the API. Consideration will need to be given to extending this period if active metabolites with longer half-lives are produced and under some other circumstances. For example, if the elimination rate of the product has high variability between subjects, the wash-out period may be longer to allow for the slower elimination in subjects with lower elimination rates. Just prior to administration of treatment during the second study period, blood samples are collected and assayed to determine the concentration of the API or metabolites. The minimum wash-out period should be at least seven days. The adequacy of the wash-out period can be estimated from the pre-dose concentration of the API and should be less than 5% of C_{max}.

If the cross-over study is problematic, a pharmacokinetic bioequivalence study with a parallel design may be more appropriate. For both cross-over and parallel-design studies, sample collection time should be adequate to ensure completion of gastrointestinal transit (approximately 2–3 days). Blood sampling up to 72 hours following administration should be carried out, unless shorter periods can be justified.

It should be noted, however, that under certain circumstances an alternative, well-established and statistically appropriate study design may be more suitable.

5.4. Alternative study designs for studies in patients

For APIs that are very potent or too toxic to administer in the highest strength to healthy volunteers (e.g. because of the potential for serious adverse events or because the trial necessitates a high dose), it is recommended that the study be conducted using the API at a lower strength in healthy volunteers. For APIs that show unacceptable pharmacological effects in healthy volunteers, even at lower strengths, a study conducted in patients may be required. Depending on the dosing posology this may be a multiple-dose, steady-state study. As above, such studies should employ a cross-over design if possible; however, a parallel group design study in patients may be required in some situations. The use of such an

alternative study design should be fully justified by the sponsor and should include patients whose disease process is stable for the duration of the bioequivalence study if possible.

5.5. Considerations for active pharmaceutical ingredients with long elimination half-lives

A single-dose, cross-over bioequivalence study for an orally-administered product with a long elimination half-life is preferred, provided an adequate washout period between administrations of the treatments is possible. The interval between study days should be long enough to permit elimination of essentially all of the previous dose from the body. Ideally the interval should not be less than five terminal elimination half-lives of the active compound or metabolite, if the latter is measured. If the cross-over study is problematic owing to a very long elimination half-life, a bioequivalence study with a parallel design may be more appropriate. A parallel design may also be necessary when comparing some depot formulations.

For both cross-over and parallel-design studies of oral products, sample collection time should be adequate to ensure completion of gastrointestinal (GI) transit (approximately 2–3 days) of the pharmaceutical product and absorption of the API. Blood sampling should be conducted for up to 72 hours following administration, but sampling beyond this time is not generally necessary for immediate-release products.

The number of subjects should be derived from statistical calculations, but generally more subjects are needed for a parallel study design than for a cross-over study design.

5.6. Consideration of multiple-dose study

In certain situations, multiple-dose studies may be considered appropriate. Multiple-dose studies in patients are most useful in cases where the medicine being studied is considered to be too potent and/or too toxic to be administered to healthy volunteers, even in single doses. In this case, a multiple-dose, cross-over study in patients may be performed without interrupting therapy. The dosage regimen used in multiple-dose studies should follow the usual dosage recommendations. Other situations in which multiple-dose studies may be appropriate are as follows:

- drugs that exhibit non-linear kinetics at a steady state (e.g., saturable metabolism, active secretion);
- cases where the assay sensitivity is too low to adequately characterize the pharmacokinetic profile after a single dose; or,
- extended-release dosage forms with a tendency to accumulation (in addition to a single-dose study).

In steady-state studies, the wash-out of the last dose of the previous treatment can overlap with the approach to steady state of the second treatment, provided the approach period is sufficiently long (at least three times the terminal half-life). Appropriate dosage administration and sampling should be carried out to document for the attainment of a steady state.

5.7. Considerations for modified release products

Modified-release products include extended-release products and delayed-release products. Extended-release products are variously known as controlled-release, prolonged-release, and sustained-release products.

Owing to the more complex nature of modified-release products relative to immediate-release products, additional data are required to ensure the bioequivalence of two modified-release products. Factors such as the coadministration of food, which influences API bioavailability and also, in certain cases, bioequivalence, must be taken into consideration. The presence of food can affect product performance both by influencing the release of the API from the formulation and by causing physiological changes in the GI tract. In this regard a significant concern with regard to modified-release products is the possibility that food may trigger a sudden and abrupt release of the API leading to "dose dumping". This would most likely be manifested as a premature and abrupt rise in the plasma concentration time profile. Therefore, bioequivalence studies conducted under both fasted and fed conditions are required for orally administered, modified-release pharmaceutical products.

Unless single-dose studies are not possible for reasons such as those discussed in section 5.4 above, single-dose, cross-over bioequivalence studies conducted under both fasted and fed conditions comparing the highest strength of the multisource product and the comparator product must be performed to demonstrate bioequivalence. Single-dose studies are preferred to multiple-dose studies as single-dose studies are considered to provide more sensitive measurement of the release of API from the pharmaceutical product into the systemic circulation. In addition to single-dose studies, multiple-dose studies may be considered for extended-release dosage forms with a tendency to accumulate, e.g. after a single dose of the highest strength the AUC for the dosing interval covers < 90% of AUC extrapolated to infinity.

The comparator product in these studies should be a pharmaceutically equivalent, modified-release product. The bioequivalence criteria for modified-release products are essentially the same as for conventional-release dosage forms except that acceptance criteria should also be applied to C_{min} (C_{tau}) in the case of multiple-dose studies. As release mechanisms of pharmaceutical products become more complex, e.g. products with an immediate-release and modified-release component, additional parameters such as partial AUC measures may be necessary to ensure the bioequivalence of two products.

The fed-state bioequivalence study should be conducted after the administration of an appropriate standardized meal at a specified time (usually not more than 30 minutes) before taking the pharmaceutical product. A meal that will promote the greatest change in GI tract conditions relative to the fasted state should be given. See section 7.4.3 for more recommendations for the content of the meal. The composition of the meal should take local diet and customs into consideration. The composition and caloric breakdown of the test meal should be provided in the study protocol and report. [Applicant may consult WHO TRS 992, Annex 7].

5.8. Subjects

5.8.1. Number of subjects

The number of subjects to be recruited for the study should be estimated by considering the standards that must be met.

The number of subjects required for a bioequivalence study is determined by:

- the error variance (coefficient of variation) associated with the primary parameters to be studied, as estimated from a pilot experiment, from previous studies or from published data;
- the significance level desired (5%);
- the statistical power desired;
- the mean deviation from the comparator product compatible with bioequivalence and with safety and efficacy;
- the need for the 90% confidence interval around the geometric mean ratio to be within bioequivalence limits, normally 80–125%, for log-transformed data.

It should be recruited for the study should be estimated by considering the standards that must be met using an appropriate method (see statistical analysis and acceptance criteria below). In addition, a number of extra subjects should be recruited, dosed appropriately, and their samples analysed based on the expected rate of drop-outs and/or withdrawals, which depends on the safety and tolerability profile of the API. The number of subjects recruited should always be justified by the sample-size calculation provided in the study protocol. The number of subjects recruited should always be justified by the sample-size calculation provided in the study protocol. A minimum of 12 subjects is required.

5.8.2. Drop-outs and withdrawals

Sponsors should select a sufficient number of study subjects to allow for possible drop-outs or withdrawals. Because replacement of subjects during the study could complicate the statistical model and analysis, drop-outs generally should not be replaced. Reasons for withdrawal (e.g., adverse drug reaction or personal reasons) must be reported. If a subject is withdrawn due to an adverse event after receiving at least one dose of the study medication the subject's plasma/serum concentration data should be provided.

Sponsors who wish to replace drop-outs during the study or consider an add-on design should indicate this intention in the protocol. It is appropriate to recruit into the study more subjects than the sample-size calculation requires. These subjects are designated as extras. The protocol should state whether samples from these extra subjects will be assayed if not required for statistical analysis.

If the bioequivalence study was performed with the appropriate number of subjects but bioequivalence cannot be demonstrated because of a larger than expected random variation or a relative difference, an add-on subject study can be performed using not less than half the number of subjects in the initial study, provided this eventuality was anticipated and provided for in the study protocol. Combining data is acceptable only in the case that the same protocol was used and preparations from the same batches were used. Add-on designs must be carried out strictly according to the study protocol and SOPs and must be given appropriate statistical treatment.

5.8.3. Selection of subjects

Pharmacokinetic bioequivalence studies should generally be performed with healthy volunteers. Clear criteria for inclusion and exclusion should be stated in the study protocol. If the pharmaceutical product is intended for use in both sexes, the sponsor may wish to include both males and females in the study. The risk to women will need to be considered on an individual basis and, if necessary, they should be warned of any possible dangers to the fetus should they become pregnant. The investigators should ensure that female volunteers are not pregnant or likely to become pregnant during the study. Confirmation should be obtained by urine tests just before administration of the first and last doses of the product under study.

Generally, subjects should be between the ages of 18 and 55 years, and their weight should be within the normal range with a body mass index (BMI) between 18 and 30 kg/m^2. The subjects should have no history of alcohol or drug abuse problems and should preferably be non-smokers. The volunteers should be screened for their suitability using standard laboratory tests, a medical history, and a physical examination. If necessary, special medical investigations may be carried out before and during studies depending on the pharmacology of the individual API being investigated, e.g., an electrocardiogram if the API has a cardiac effect. The ability of the volunteers to understand and comply with the study protocol has to be assessed. Subjects who are being or have previously been treated for any gastrointestinal problems, or convulsive, depressive, or hepatic disorders, and in whom there is a risk of a recurrence during the study period, should be excluded.

If a parallel-design study is planned, standardization of the two groups of subjects is important in order to minimize variation not attributable to the investigational products.

If the aim of the bioequivalence study is to address specific questions(e.g. bioequivalence in a special population) the selection criteria should be adjusted accordingly.

5.8.4. Monitoring the health of subjects during the study

During the study, the health of volunteers should be monitored so that onset of side-effects, toxicity, or any inter-current disease may be recorded and appropriate measures taken. The incidence, severity, and duration of any adverse reactions and side-effects observed during the study must be reported. The probability that an adverse event is due to the FPP should be judged by the investigator.

Health monitoring before, during and after the study must be carried out under the supervision of a qualified medical practitioner licensed in the jurisdiction in which the study is conducted.

5.8.5. Study standardization

Standardization of study conditions is important to minimize the magnitude of variability other than in the pharmaceutical products. Standardization should cover exercise, diet, fluid intake, posture, and the restriction of the intake of alcohol, caffeine, certain fruit juices, and concomitant medicines for a specified time period before and during the study.

Volunteers should not take any other medicine, alcoholic beverages, or over the-counter (OTC) medicines and supplements for an appropriate interval either before or during the study. In the event of an emergency, the use of any non-study medicine must be reported (dose and time of administration).

Physical activity and posture should be standardized as far as possible to limit their effects on gastrointestinal blood flow and motility. The same pattern of posture and activity should be maintained for each day of the study. The time of day at which the study drug is to be administered should be specified.

Study medicines are usually given after an overnight fast of at least 10 hours, and participants are allowed free access to water. On the morning of the study, no water is allowed during the hour prior to drug administration. The dose should be taken with a standard volume of water (usually 150–250 ml). Two hours after drug administration, water is again permitted. A standard meal is usually provided four hours after drug administration.

All meals should be standardized, and the composition stated in the study protocol and report. Some medicines are normally given with food to reduce gastrointestinal side-effects; in certain cases, co-administration with food increases bioavailability of orally administered preparations. If the labeling states that the pharmaceutical product should be taken with food, then a fed study should be used to assess bioequivalence. Fed state studies are also required in bioequivalence studies of modified release formulations (see above under 4.5 of this guideline). The test meal selected should be consumed within 20 minutes. The product should be administered according to the protocol and within 30 minutes after the meal has been eaten.

5.9. Investigational product

5.9.1. Multisource pharmaceutical product (test product)

The multisource pharmaceutical product used in the bioequivalence studies for registration purposes should be identical to the proposed commercial pharmaceutical product. Therefore, not only the composition and quality characteristics (including stability), but also the manufacturing methods (including equipment and procedures) should be the same as those to be used in the future routine production runs. Test products must be manufactured under GMP regulations. Batch-control results of the multisource product, and the lot numbers and expiry dates of both multisource and comparator products should be stated in the protocol and report.

Samples should ideally be taken from batches of industrial scale. When this is not feasible, pilot- or small-scale production batches may be used, provided that they are not smaller than 10% of expected full production batches, or 100,000 units, whichever is higher (unless otherwise justified), and are produced with the same formulation, similar equipment, and process as that planned for commercial production batches. If the product is subjected to further scale-up, this should be properly validated. A biobatch of less than 100 000 units may be accepted provided that this is the proposed production batch size, with the understanding

that future scale-up for production batches will not be accepted unless supported by invitro and/or in vivo data as applicable.

It is recommended that potency and in vitro dissolution characteristics of the multisource and comparator pharmaceutical products be ascertained prior to performance of an equivalence study. Content of the API(s) of the comparator product should be close to the label claim, and the difference between two products (multisource & comparator products) should preferably be not more than ±5%. If, because of the lack of availability of different batches of the comparator product, it is not possible to study batches with potencies within ± 5%, potency correction maybe required on the statistical results from the bioequivalence study.

5.10. Choice of comparator product

The choice of comparator product should be justified by the applicant. The country of origin of the comparator product should be reported together with lot number and expiry date. The country of origin of the comparator product should be from a well-regulated market and should be traceable, whenever required.

The innovator pharmaceutical product is usually the most logical comparator product for a multisource pharmaceutical product because its quality, safety, and efficacy have been well documented in pre-marketing studies and post-marketing monitoring schemes.

A generic pharmaceutical product should not be used as a comparator as long as an innovator pharmaceutical product is available, because this could lead to progressively less reliable similarity of future multisource products and potentially to a lack of inter-changeability with the innovator.

The comparator product can be a similar, pharmaceutically equivalent product (see below), such as:

a) an innovator product registered with the Authority and/or SRAs and can be registered with the Authority;
b) a generic product registered with SRAs which has been accepted by the Authority
c) a selection of comparator made through a consult by the applicant with the Authority.

Applicant may consult WHO Technical Report Series No. 992, 2015 Annex 8 and WHO Technical Report Series No. 1003, 2017 Annex 5 for guidance for the selection of comparator product.

5.11. Study conduct

5.11.1. Selection of dose

In bioequivalence studies, the molar equivalent dose of multisource and comparator product must be used.

For a series of strengths that can be considered proportionally formulated, the strength with the greatest sensitivity for bioequivalence assessment should be administered as a single unit.

This will usually be the highest marketed strength. A higher dose i.e., more than one dosage unit may be employed when analytical difficulties exist. In this case, the total single dose should not exceed the maximum daily dose of the dosage regimen. Alternatively, the application of area under the curve (AUC) truncated to 3 × median t_{max} of the comparator formulation would avoid problems of lack of assay sensitivity. In certain cases, a study performed with a lower strength can be considered acceptable if this lower strength is chosen for reasons of safety or if the API is highly soluble and its pharmacokinetics are linear over the therapeutic range.

5.11.2. Non-linear pharmacokinetics

When the API in a series of strengths, which are considered proportionally formulated, exhibits non-linear pharmacokinetics over the range of strengths, special consideration is necessary when selecting the strength for study.

- For APIs exhibiting non-linear pharmacokinetics within the range of strengths resulting in greater than proportional increases in AUC with increasing dose, the comparative bioavailability study should be conducted on at least the highest marketed strength.
- For APIs with non-linear pharmacokinetics within the range of strengths due to saturable absorption and resulting in less than proportional increases in AUC with increasing dose, the bioequivalence study should be conducted on at least the lowest strength (or a strength in the linear range).
- For APIs with non-linear pharmacokinetics within the range of strengths due to limited solubility of the API and resulting in less than proportional increases in AUC with increasing dose, bioequivalence studies should be conducted on at least the lowest strength (or a strength in the linear range) and the highest strength.

5.11.3. Sampling times

Blood samples should be taken at a frequency sufficient for assessing C_{max}, AUC, and other parameters. Sampling points should include a pre-dose sample, at least 1–2 points before C_{max}, 2 points around C_{max}, and 3–4 points during the elimination phase. Consequently, at least seven sampling points will be necessary for estimation of the required pharmacokinetic parameters.

For most medicines, the number of samples necessary will be higher to compensate for between-subject differences in absorption and elimination rate and, thus, enable accurate determination of the maximum concentration of the API in the blood (C_{max}) and terminal elimination rate constant in all subjects. Generally, sampling should continue for long enough to ensure that 80% of the AUC (0→infinity) can be accrued, usually up to 72 hours. The exact duration of sample collection depends on the nature of the API and the input function from the administered dosage form.

5.11.4. Sample fluids and their collection

Under normal circumstances, blood should be the biological fluid sampled to measure the concentrations of the API. In most cases, the API or its metabolites are measured in serum or plasma. If the API is excreted predominantly unchanged in the urine, urine can be sampled. The volume of each sample must be measured at the study center, where possible,

immediately after collection, and included in the report. The number of samples should be sufficient to allow the estimation of pharmacokinetic parameters. However, in most cases, the exclusive use of urine-excretion data should be avoided as this does not allow estimation of the t_{max} and the maximum concentration.

Blood samples should be processed and stored under conditions that have been shown not to cause degradation of the analytes. This can be proven by analyzing duplicate quality control samples during the analytical period. Quality control samples must be prepared in the fluid of interest (e.g., plasma) including concentrations, at least, at the low, middle, and high segments of the calibration range. The quality control samples must be stored with the study samples and analyzed with each set of study samples for each analytical run. The sample collection methodology must be specified in the study protocol.

5.11.5. Parameters to be assessed

In bioavailability studies, the shape and area under the plasma concentration versus time curves are mostly used to assess rate (C_{max}, t_{max}) and extent (AUC)of exposure. Sampling points or periods should be chosen such that the concentration-versus-time profile is adequately defined to allow calculation of relevant parameters. For single-dose studies, the following parameters should be measured or calculated:

- Area under the plasma/serum/blood concentration–time curve from time zero to time t (AUC0–t), where tis the last sampling time point with measurable concentration of the API in the individual formulation tested. The method of calculating AUC values should be specified. In general, AUC should be calculated using the linear/log trapezoidal integration method. Non-compartmental methods should be used for pharmacokinetic calculations in bioequivalence studies;
- C_{max} is the maximum or peak concentration observed representing peak exposure of API (or metabolite) in plasma, serum, or whole blood.

UsuallyAUC_{0-t} and C_{max} are considered to be the most relevant parameters for assessment of bioequivalence. In addition, it is recommended that the following parameters be estimated:

- area under the plasma/serum/blood concentration–time curve from time zero to time infinity ($AUC_{0-\infty}$), representing total exposure, where $AUC_{0-\infty} = AUC_{0-t} + C_{last}/K_e$; C_{last} is the last measurable drug concentration and K_e is the terminal or elimination rate constant calculated according to an appropriate method;
- t_{max} is the time after administration of the drug at which C_{max} is observed; for

For additional information the elimination parameters can be calculated; and,

- $T_{1/2}$ is the plasma (serum, whole blood) half-life.

For multiple-dose studies conducted with modified-release products, the following parameters should be calculated:

- AUC_{τ} is AUC over one dosing interval (τ) at steady-state;
- C_{max};

- C_{min} (C_{tau}) is concentration at the end of a dosing interval; and,
- Peak trough fluctuation is the percentage difference between $C_{max}$and C_{min}.

As release mechanisms of pharmaceutical products become more complex, e.g. products with an immediate-release and a modified-release component, additional parameters such as partial AUC measures may be necessary to ensure the bioequivalence of two products.

When urine samples are used, cumulative urinary recovery (Ae) and maximum urinary excretion rate are employed instead of AUC and C_{max}.

5.11.6. Studies of metabolites

Generally, evaluation of pharmacokinetic bioequivalence will be based upon the measured concentrations of the parent drug released from the dosage form rather than the metabolite. The concentration–time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution, and elimination.

In rare cases, it may be necessary to measure metabolite concentrations of a primary active metabolite rather than those of the parent drug:

- The measurement of concentrations of a therapeutically active metabolite is acceptable if the substance studied is a pro-drug; and,
- Measurement of a metabolite may be preferred when concentrations of the parent drug are too low to allow reliable analytical measurement in blood, plasma, or serum for an adequate length of time, or when the parent compound is unstable in the biological matrix.

It is important to decide beforehand and state in the study protocol, which chemical entities (API or metabolite) will be analysed in the samples and to identify the analyte whose data will be used to assess bioequivalence.

When measuring the active metabolites, wash-out period and sampling times may need to be adjusted to enable adequate characterization of the pharmacokinetic profile of the metabolite.

5.11.7. Measurement of individual enantiomers

A non-stereo selective assay is currently acceptable for most pharmacokinetic bioequivalence studies. When the enantiomers have very different pharmacological or metabolic profiles, assays that distinguish between the enantiomers of a chiral API may be appropriate. Stereo selective assay is also preferred when systemic availability of different enantiomers is demonstrated to be non-linear.

5.11.8. Use of fed-state studies in bioequivalence determination

5.11.8.1. Immediate-release formulations

Fasted-state studies are generally preferred. When the product is known to cause gastrointestinal disturbances if given to subjects in the fasted state, or if labeling restricts administration to subjects in the fed state, then the fed-state pharmacokinetic bioequivalence study becomes the preferred approach.

5.11.8.2. Modified-release formulations

In addition to a study conducted under fasted conditions, food-effect studies are necessary for all multisource, modified-release formulations to ensure that the interaction between the varying conditions in the GI tract and the product formulations does not differentially impact the performance of the multisource and comparator products. The presence of food can affect product performance both by influencing the release of the API from the formulation and by causing physiological changes in the GI tract. A significant concern with regard tomodified-release products is the possibility that food may trigger a sudden andabrupt release of the API leading to “dose dumping”.

In these cases, the objective is to select a meal that will challenge the robustness of the new multisource formulation to prandial effects on bioavailability. To achieve this, a meal that will provide a maximal perturbation to the GI tract relative to the fasted state should be employed, e.g. a high-fat (approximately50% of the total caloric content of the meal), high-calorie (approximately 800to 1000 kilocalories) test meal has been recommended (2). The meal selected should take into account local customs and diet. The caloric breakdown of thetest meal should be provided in the study report.

The subject should start eating the meal 30 minutes before the FPP is administered and complete eating the meal prior to FPP administration.

5.11.9. Quantification of active pharmaceutical ingredient

All analytical test methods used to determine the active compound and/or its biotransformation product in the biological fluid must be well characterized, fully validated, and documented. The objective of the validation is to demonstrate that a particular method used for quantitative measurement of analytes in a given biological matrix, such as blood, plasma, serum or urine, is reliable and reproducible for the intended use.

Bioanalytical methods should meet the requirements of selectivity, lower limit of quantification, the response function and calibration range (calibration curve performance), specificity, accuracy, precision, stability of the analyte(s) in the biological matrix, stability of the analyte(s) and of the internal standard in the stock and working solutions, and in extracts throughout the entire period of storage and processing conditions.

In general:

- the analytical method should be able to differentiate the analyte(s)of interest and, if employed, the internal standard (IS) from endogenous components in the matrix or other components in the sample;

- the lower limit of quantification (LLOQ), being the lowest concentration of analyte in a sample, should be estimated to prove that the analyte at this concentration can be quantified reliably, with an acceptable accuracy and precision;
- the response of the instrument with regard to the concentration of analyte should be known and should be evaluated over a specified concentration range. The calibration curve should be prepared in the same matrix as the matrix of the intended subject samples by spiking the blank matrix with known concentrations of the analyte. A calibration curve should consist of a blank sample, a zero sample and 6–8 non-zero samples covering the expected range;
- within-run and between-run accuracy and precision should be assessed on samples spiked with known amounts of the analyte, the QC samples, at a minimum of three different concentrations;
- matrix effects should be investigated when using mass spectrometric methods;
- stability of the analyte in the stock solution and in the matrix should be proven covering every step taken during sample preparation and sample analysis, as well as the storage conditions used;
- when more than one analyte is present in subject samples, it is recommended to demonstrate the stability of the analytes in the matrix in the presence of the other analytes under standard conditions such as freeze−thaw testing, short-term room temperature storage and long-term freezer storage;
- where changes are made to an analytical method that has already been validated, a full validation may not be necessary depending on the nature of the changes implemented. A partial validation maybe acceptable;
- a cross-validation is needed in cases where data are obtained from different methods within and across studies or when data are obtained within a study from different laboratories applying the same method;
- analysis of subject samples should be carried out after validation of the analytical method. Before the start of the analysis of the subject samples, the performance of the bioanalytical method should have been verified;
- calibration and QC standards should be processed in an identical manner and at the same time as the subjects' samples from the same run;
- reasons for reanalysis, reinjection and reintegration of subject samples should be predefined in the protocol, study plan or SOP. Reinjection of a full analytical run or of individual calibration standard samples or QC samples, simply because the calibration or QCs failed, without any identified analytical cause, is considered unacceptable. For bioequivalence studies, reanalysis, reinjection or reintegration of subject samples for reasons related to pharmacokinetic fit is normally not acceptable as this may affect and bias the outcome of such a study;
- when analysing subject samples, the precision and accuracy of the method should be confirmed by reanalysing subject samples in a separate analytical run on a different day (incurred samples reanalysis (ISR)). ISR should be performed for each bioequivalence trial. The extent of testing done should be based on an in-depth understanding of the analytical method and analyte used;
- the samples from one subject (all periods) should be analysed in the same analytical run if possible.

Some of the important recommendations are:

- Validation comprises pre-study and within-study phases. During the pre-study phase, stability of the stock solution and spiked samples in the biological matrix, specificity,

sensitivity, accuracy, precision and reproducibility should be provided. Within-study validation proves the stability of samples collected during a clinical trial under storage conditions and confirms the accuracy and precision of the determinations.

- Validation must cover the intended use of the assay.
- The calibration range must be appropriate to the study samples. A calibration curve should be prepared in the same biological matrix as will be used for the samples in the intended study by spiking the matrix with known concentrations of the analyte. A calibration curve should consist of a blank sample, a zero sample, and 6–8 non-zero samples covering the expected range. Concentrations of standards should be chosen on the basis of the concentration range expected in a particular study.
- If an assay is to be used at different sites, it must be validated at each site, and cross-site comparability established.
- An assay which is not in regular use requires sufficient revalidation to show that it still performs according to the original validated test procedures.
- The revalidation study must be documented, usually as an appendix to the study report.
- Within a study, the use of two or more methods to assay samples in the same matrix over a similar calibration range is strongly discouraged.
- If different studies are to be compared and the samples from the different studies have been assayed by different methods, and the methods cover a similar concentration range and the same matrix, then the methods should be cross-validated.
- Spiked quality control samples at a minimum of three different concentrations in duplicate should be used for accepting or rejecting the analytical run.
- All the samples from one subject (all periods) should be analyzed in the same analytical run, if possible.

Validation procedures, methodology, and acceptance criteria should be specified in the analytical protocol, and/or the SOP. All experiments used to support claims or draw conclusions about the validity of the method should be described in a report (method validation report). Any modification of the method during the analysis of study samples will require adequate revalidation.

The results of study sample determination should be given in the analytical report together with calibration and quality control sample results, repeat analyses (if any), and a representative number of sample chromatograms.
Applicant may consult WHO TRS 992, annex 7 for detail requirements of bioanalytical methods.

5.11.10. Statistical analysis

The primary concern in bioequivalence assessment is to limit the risk of a false declaration of equivalence. Statistical analysis of the bioequivalence trial should demonstrate that a clinically significant difference in bioavailability between the multisource product and the

comparator product is unlikely. The statistical procedures should be specified in the protocol before the data collection starts.
The statistical method for testing pharmacokinetic bioequivalence is based upon the determination of the 90% confidence interval around the ratio of the log-transformed population means (multisource/comparator) for the pharmacokinetic parameters under consideration, and by carrying out two one-sided tests at the 5% level of significance. To establish pharmacokinetic bioequivalence, the calculated confidence interval should fall within a preset bioequivalence limit. The procedures should lead to a decision scheme which is symmetrical with respect to the two formulations (i.e., leading to the same decision, whether the multisource formulation is compared to the comparator product or the comparator product to the multisource formulation).

All concentration-dependent pharmacokinetic parameters (e.g., AUC and C_{max}) should be log-transformed using either common logarithms to the base 10 or natural logarithms. The choice of common or natural logs should be consistent and should be stated in the study report.

Logarithmically transformed, concentration-dependent pharmacokinetic parameters should be analyzed using analysis of variance (ANOVA). Usually the ANOVA model includes the formulation, period, sequence or carry-over, and subject factors.

Parametric methods, i.e., those based on normal distribution theory, are recommended for the analysis of log-transformed bioequivalence measures.

The general approach is to construct a 90% confidence interval for the quantity $\mu T - \mu R$ and to reach a conclusion of pharmacokinetic equivalence if this confidence interval is within the stated limits. The nature of parametric confidence intervals means that this is equivalent to carrying out two one-sided tests of the hypothesis at the 5% level of significance. The antilogs of the confidence limits obtained constitute the 90% confidence interval for the ratio of the geometric means between the multisource and comparator products.

The same procedure should be used for analyzing parameters from steady-state trials or cumulative-urinary recovery, if required.

For t_{max}, descriptive statistics should be given. If t_{max} is to be subjected to a statistical analysis, this should be based on non-parametric methods and should be applied to untransformed data. A sufficient number of samples around predicted maximal concentrations should have been taken to improve the accuracy of the t_{max} estimate. For parameters describing the elimination phase ($T_{1/2}$), only descriptive statistics should be given.

Methods for identifying and handling of possible outlier data should be specified in the protocol. Medical or pharmacokinetic explanations for such observations should be sought and discussed. As outliers may be indicative of product failure, post hoc deletion of outlier

values is generally discouraged. An approach to dealing with data containing outliers is to apply distribution-free (non-parametric) statistical methods.

If the distribution of log-transformed data is not normal, non-parametric statistical methods can be considered. The justification of the intent to use non-parametric statistical methods should be included a priori in the protocol.

5.11.11. Acceptance ranges

5.11.11.1. Area under the curve ratio

The 90% confidence interval for this measure of relative bioavailability should lie within a bioequivalence range of 0.80–1.25.
If the API is determined to possess a narrow therapeutic index (NTI) the bioequivalence acceptance range should be restricted 90.00–111.11%.

The same criterion applies to the parameter AUCτ in multiple-dose studies and for partial AUCs if they are necessary for comparative testing of a modified-release product.

5.11.11.2. C_{max} ratio

In general, the acceptance limit 0.80–1.25 should be applied to the C_{max} ratio. However, this measure of relative bioavailability is inherently more variable than, for example, the AUC ratio and, in certain cases, a wider acceptance range (e.g., 0.75–1.33) may be acceptable. The range used must be defined prospectively and should be justified, taking into account safety and efficacy considerations. In exceptional cases, a simple requirement for the point estimate to fall within bioequivalence limits of 0.80–1.25 may be acceptable with appropriate justification in terms of safety and efficacy.

If the API is determined to possess a narrow therapeutic index, the bioequivalence acceptance range may need to be restricted to 90.00–111.11%, if appropriate.

The same criterion applies to the parameters C_{max} and C_{tau} in multiple-dose studies.

5.11.11.3. t_{max} difference

Statistical evaluation of t_{max} makes sense only if there is a clinically relevant claim for rapid onset of action or concerns about adverse effects. The nonparametric 90% confidence interval for this measure of relative bioavailability should lie within a clinically relevant range.

For other pharmacokinetic parameters, the same considerations as outlined above apply.

5.11.12. Reporting of results

The report of a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation, complying with the rules of good clinical practices. The relevant ICH Guideline, (www.ich.org) can be used in the preparation of the study report. The responsible

investigator(s) should sign their respective sections of the report. Names and affiliations of the responsible investigator(s), site of the study, and period of its implementation should be stated. The names and batch numbers of the pharmaceutical products used in the study as well as the composition(s) of the tests product(s) should be given. This should be provided in Module 5 of the PD. Results of in vitro dissolution tests should be provided either in Module 3 or Module 5 of the PD. In addition, the applicant should submit a signed statement confirming that the test product is identical to the pharmaceutical product that is submitted for registration.

The bioanalytical validation report should be attached. The bioanalytical report should include the data on calibrations and quality control samples. A representative number of chromatograms or other raw data should be included covering the whole calibration range, quality control samples, and specimens from the clinical trial. All results should be presented clearly. All concentrations measured in each subject and the sampling time should be tabulated for each formulation. Tabulated results showing API concentration analyses according to analytical run (including runs excluded from further calculations, including all calibration standards and quality control samples from the respective run) should also be presented. The tabulated results should present the date of run, subject, study period, product administered (multisource or comparator), and time elapsed between drug application and blood sampling in a clear format. The procedure for calculating the parameters used (e.g., AUC) from the raw data should be stated. Any deletion of data should be justified.

If results are calculated using pharmacokinetic models, the model and the computing procedure used should be justified. Individual blood concentration/time curves should be plotted on a linear/linear and log/linear scale. All individual data and results should be given, including information on those subjects who dropped out. The drop-outs and/or withdrawn subjects should be reported and accounted for.

Results of all measured and calculated pharmacokinetic parameters should be tabulated for each subject–formulation combination, together with descriptive statistics. The statistical report should be sufficiently detailed to enable the statistical analyses to be repeated, if necessary. If the statistical methods applied deviate from those specified in the trial protocol, the reasons for the deviations should be stated.

5.11.13. Special considerations

5.11.13.1. Fixed-dose combination products

If the pharmacokinetic bioequivalence of fixed-dose combination (FDC) products is assessed by in vivo studies, the study design should follow the same general principles as described above. The multisource FDC product should be compared with the pharmaceutically equivalent comparator FDC product. In certain cases (e.g., when no comparator FDC product is available on the market), separate products administered in free combination can be used as a comparator. Sampling times should be chosen to enable the pharmacokinetic parameters of all APIs to be adequately assessed. The bioanalytical method should be validated with respect to all compounds measured. Statistical analyses should be performed with pharmacokinetic

data collected on all active ingredients; the 90% confidence intervals of test/comparator ratio of all active ingredients should be within acceptance limits.

5.11.13.2. Clinically important variations in bioavailability

Innovators should make all efforts to provide formulations with good bioavailability characteristics. If a better formulation is developed over time by the innovator, this should then serve as the comparator product. A new formulation with a bioavailability outside the acceptance range for an existing pharmaceutical product is not interchangeable by definition. Adjusting the strength to compensate, with regard to sub- or supra-bioavailability in comparison with the comparator product, is beyond the scope of this document, as the prerequisite for pharmaceutical equivalence is not fulfilled.

5.11.13.3. "Highly variable drugs"

A "highly variable drug" has been defined as an API with a within-subject variability of ≥ 30% in terms of the ANOVA-CV. Moreover, "highly variable drugs" are generally safe drugs with shallow dose–response curves. Proving the bioequivalence of medicinal products containing "highly variable drugs" is problematic because the higher the ANOVA-CV, the wider the 90% confidence interval. Thus, large numbers of subjects must be enrolled in studies involving highly variable drugs to achieve adequate statistical power.

The following approaches to this problem can be applied:

- Wider bioequivalence limits of 0.75–1.33 can be acceptable, provided there is adequate justification taking into consideration the therapeutic category of the drug.
- Products are considered to be bioequivalent, if the 90% confidence interval of average ratios of AUC and C_{max} between test and reference products is within the acceptable range of 0.8–1.25; if the confidence interval is not in the acceptable range, test products are accepted as bioequivalent, if the following three conditions are satisfied:
  - the total sample size of the initial bioequivalence study is not less than 20 (n = 10/group), or pooled sample-size of the initial and add-on subject studies is not less than 30;
  - the ratio of geometric least-squares means of AUC and C_{max} between the multisource and comparator product are between 0.9 and 1.11, and dissolution rates of test and comparator products are evaluated to be equivalent under all dissolution testing conditions (*See appendix 3*); and,
  - this rule cannot be applied to slowly dissolving products from which less than 80% of a drug dissolves within the final testing time (2 hours in pH 1.2medium and 6 hours in others) under any conditions of the dissolution tests described.

The extent of the widening of the acceptance interval for C_{max} is defined based upon the intrasubject variability seen in the bioequivalence study using scaled-average-bioequivalence according to $[U, L] = \exp[\pm k \cdot sWR]$, where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and sWR is the intrasubject standard deviation of the log-transformed values of C_{max} of the reference

product. The below table gives examples of how different levels of variability lead to different acceptance limits using this methodology.

Acceptance limits for different levels of variability

Intrasubject CV (%)	Lower limit	Upper limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥50	69.84	143.19

$$\boldsymbol{CV}(\%) = \sqrt{\left(\boldsymbol{e}^{\boldsymbol{s_{WR}}^{\boldsymbol{2}}}\right) - \boldsymbol{1}}$$

The geometric mean ratio (GMR) for C_{max} should lie within the conventional acceptance range 80.00–125.00%.

6. Pharmacodynamics studies

Studies in healthy volunteers or patients using pharmacodynamics measurements may be used for establishing equivalence between two pharmaceutical products. Pharmacodynamics studies are not recommended for orally administered pharmaceutical products for systemic action when the API is absorbed into the systemic circulation and a pharmacokinetic approach can be used to assess systemic exposure and establish bioequivalence. This is because variability in pharmacodynamics measures is always greater than that in pharmacokinetic measures. In addition, pharmacodynamics measures are often subject to significant placebo effects, which add to the variability and complicate experimental design. Pharmacodynamic bioequivalence studies may become necessary if quantitative analysis of the API and/or metabolite(s) in plasma or urine cannot be made with sufficient accuracy and sensitivity. Furthermore, pharmacodynamic bioequivalence studies in humans are required if measurements of API concentrations cannot be used as surrogate end-points for the demonstration of efficacy and safety of the particular pharmaceutical product.

In certain treatment categories, such as pharmaceutical products designed to act locally, there is no realistic alternative to performing pharmacodynamic bioequivalence studies. Therefore, pharmacodynamic bioequivalence studies may be appropriate for pharmaceutical products administered topically and for inhalation dosage forms.

If pharmacodynamics studies are to be used, they must be performed as rigorously as bioequivalence studies, and the principles of current GCP must be followed.

The following requirements must be recognized when planning, conducting, and assessing the results of a study intended to demonstrate equivalence by measuring pharmacodynamic drug responses:

- The response measured should be a pharmacological or therapeutic effect which is relevant to the claims of efficacy and/or safety.
- The methodology must be validated for precision, accuracy, reproducibility, and specificity.
- Neither the test product nor the comparator product should produce a maximal response in the course of the study, since it may be impossible to detect differences between formulations given in doses that give maximum or near-maximum effects. Investigation of dose–response relationships may be a necessary part of the design.
- The response should be measured quantitatively, preferably under double-blind conditions, and be recordable by an instrument that produces and records the results of repeated measurements to provide a record of the pharmacodynamic events, which are substitutes for measurements of plasma concentrations. Where such measurements are not possible, recordings on visual analogue scales may be used. Where the data are limited to qualitative (categorized) measurements appropriate special statistical analysis will be required.
- Participants should be screened prior to the study to exclude non-responders. The criteria by which responders are distinguished from non-responders must be stated in the protocol.
- In instances where an important placebo effect can occur, comparison between pharmaceutical products can only be made by a priori consideration of the potential placebo effect in the study design. This may be achieved by adding a third phase with placebo treatment in the design of the study.
- The underlying pathology and natural history of the condition must be considered in the study design. There should be knowledge of the reproducibility of baseline conditions.
- A cross-over design can be used. Where this is not appropriate, a parallel group study design should be chosen.

The selection basis for the multisource and comparator products should be the same as described above. In studies in which continuous variables can be recorded, the time-course of the intensity of the drug action can be described in the same way as in a study in which plasma concentrations are measured, and parameters can be derived that describe the area under the effect–time curve, the maximum response, and the time at which the maximum response occurred.

The statistical considerations for the assessment of the outcome of the study are, in principle, the same as those outlined for the analysis of pharmacokinetic bioequivalence studies. However, a correction for the potential non-linearity of the relationship between the dose and the area under the effect–time curve should be performed on the basis of the outcome of the dose-ranging study. It should be noted, however, that the acceptance range, as applied for bioequivalence assessment, may not be appropriate and should be justified on a case-by-case basis and defined in the protocol.

7. Clinical trials

In some instances, in vivo studies using plasma concentration time–profile data are not suitable for assessing equivalence between two formulations. Although, in some cases, pharmacodynamic bioequivalence studies can be an appropriate tool for establishing equivalence, in others, this type of study cannot be performed because of a lack of meaningful pharmacodynamic parameters that can be measured; a comparative clinical trial then has to be performed to demonstrate equivalence between two formulations.

If a clinical bioequivalence study is considered as being undertaken to prove equivalence, the same statistical principles apply as for the pharmacokinetic bioequivalence studies. The number of patients to be included in the study will depend on the variability of the target parameters and the acceptance range and is usually much higher than the number of subjects needed in pharmacokinetic bioequivalence studies.

The methodology for establishing equivalence between pharmaceutical products by means of a clinical trial in patients with a therapeutic end-point has not yet evolved as extensively as for pharmacokinetic bioequivalence trials.

Some important items that need to be defined in the protocol are:

- The target parameters that usually represent relevant clinical end-points from which the onset (if applicable and relevant) and intensity of the response are to be derived.
- The size of the acceptance range has to be defined case by case, taking into consideration the specific clinical conditions. These include, among others, the natural course of the disease, the efficacy of available treatments, and the chosen target parameter. In contrast to pharmacokinetic bioequivalence studies (where a conventional acceptance range is applied), the size of the acceptance range in clinical trials should be set individually, according to the therapeutic class and indication(s).
- The presently used statistical method is the confidence interval approach. The main concern is to rule out the possibility that the test product is inferior to the comparator pharmaceutical product by more than the specified amount. Hence, a one-sided confidence interval (for efficacy and/or safety) may be appropriate. The confidence intervals can be derived from either parametric or nonparametric methods.
- Where appropriate, a placebo leg should be included in the design.
- In some cases, it is relevant to include safety end-points in the final comparative assessments.
- The selection basis for the multisource and comparator products should be the same as described above.

8. In vitro testing

The dissolution test, at first exclusively a quality control test, is now emerging as a surrogate equivalence test for certain categories of orally administered pharmaceutical products. For these products (typically solid oral dosage forms containing APIs with suitable properties), a

comparative in vitro dissolution profile similarity can be used to document equivalence of a multisource with a comparator product (see Appendix 3).

It should be noted, dissolution tests for quality control purposes in other pharmacopoeia do not generally correspond to the test conditions required for evaluating bioequivalence of multisource products and should not be applied for this purpose.
Requirements for BCS based biowaivers on solid oral dosage forms and dose-proportionate multiple strength products are described under Guidance on waiver of in vivo bioequivalence requirements of the Authority. Applicants who wish on biowaiver based on the BCS and dose-proportionate product need follow such guidance document of the authority. WHO TRS 992 annex 7 can be used as further reference.

8.1. Biopharmaceutics Classification System

The Biopharmaceutics Classification System (BCS) is based on aqueous solubility and intestinal permeability of the drug substance. It classifies the API into one of four classes:

- Class 1: High solubility, high permeability
- Class 2: Low solubility, high permeability
- Class 3: High solubility, low permeability
- Class 4: Low solubility, low permeability

Combining the dissolution of the pharmaceutical product with these two properties of the API takes the three major factors that govern the rate and extent of drug absorption from immediate-release solid dosage forms into account. On the basis of their dissolution properties, immediate-release dosage forms can be categorized as having “very rapid,” “rapid,” or “not rapid” dissolution characteristics.

8.1.1. High solubility

An API is considered highly soluble when the highest dose recommended or highest dosage strength available on the market as an oral solid dosage form is soluble in 250 ml or less of aqueous media over the pH range of 1.2–6.8.

The pH-solubility profile of the API should be determined at 37± 1 °C in aqueous media. A minimum of three replicate determinations of solubility at each pH condition (1.2-6.8) is recommended.

8.1.2. High permeability

An API is considered highly permeable when the extent of absorption in humans is 85% or more based on a mass balance determination or in comparison with an intravenous comparator dose. Experimental evidence and/or literature reference should be used to justify the high permeability of the API.

Biowaivers for solid oral dosage forms based on BCS is described under Guidance on waiver of in vivo bioequivalence requirements, 2015 of the Authority. BCS based biowaiver for such solid oral dosage forms can be considered under the following conditions.

- Dosage forms of APIs that are highly soluble, highly permeable (BCS Class 1), and rapidly dissolving are eligible for a biowaiver, based on the BCS provided:
  - the dosage form is rapidly dissolving (as defined in Appendix 3)and the dissolution profile of the multisource product is similar to that of the comparator product at pH 1.2, pH 4.5 and pH 6.8 buffer using the paddle method at 75 rpm, or the basket method at 100 rpm, and meets the criteria of dissolution profile similarity, $f2 \geq 50$ (or equivalent statistical criterion); and,
  - if both the comparator and the multisource dosage forms are very rapidly dissolving(85% in 15 minutes), the two products are deemed equivalent and a profile comparison is not necessary.
- Dosage forms of APIs that are highly soluble and have low permeability (BCS Class 3) are eligible for biowaivers, provided they meet all the criteria defined in Appendix 3and the risk–benefit is additionally addressed in terms of extent, site, and mechanism of absorption.

8.2. Reports of dissolution profile study

The report on a dissolution study, used in the biowaiver application, should include a study protocol and, at least, the following information:

a) Purpose of study;
b) Products /batch information;
c) Batch numbers, manufacturing and expiry dates, and batch size of the test product;
d) Certificates of Analysis (CoAs) and packaging of the batches used in the study;
e) Batch manufacturing record(s) for the batch of the test product used in the comparative dissolution study;
f) Full dissolution conditions and method, as well as the number of units (tablets, capsules, etc.) per study. It should be indicated how and when the samples were filtered. Any problems with pH-related stability of samples should be indicated and discussed in terms of preventive handling measures, analysis, and interpretation of data;
g) Analytical method including validation or reference to the quality part of the dossier;
h) Results (% API dissolved) presented—
   i. Tabulated (individual results, mean and %CV),
   ii. Graphically, and,
   iii. Similarity determination /f2 calculation, if necessary and applicable; and,
i) Conclusion/recommendation.

For further dissolution profile study requirements, see Appendix 3 and WHO TRS 992 Annex 7.

ANNEX V: SAMPLE OF ACTUAL PRODUCT

Where applicable, a sample of actual products may be requested for the purpose of visual confirmation, and/or for the purpose of laboratory testing or analytical performance evaluation of the device.

Sample of actual products and reference standard substances can be submitted after document review process completed and/or along with the dossier for registration. The quantities of samples to be submitted should be stated on the letter of acceptance for the dossier.

1. The quantities of samples and reference standard substances will be as follows:

	Dosage form	**Minimum quantity**
1	Tablet	200 tablets
2	Capsule	200 capsules
3	Injectable liquids /powder for injections	100 vial/ampoules/sachets
4	Ophthalmic/ otic solutions/suspensions	80 tubes
5	Oral liquid/dry powder for suspension	60 bottles
6	Semi-solid preparations	50 units
7	Ophthalmic ointment	100 tubes
8	Rectal and vaginal preparations	50 units/suppositories
9	IV fluid	60 bags

2. Reference standards will have the following criteria:
    a. For medicines that are official in a pharmacopeia (Ph.Int., Ph.Eur., BP, USP, JP), primary standards as per its monograph with a minimum quantity of 100mg and working standard of 500mg;
    b. For medicines that are not official in a pharmacopeia (Ph.Int., Ph.Eur., BP, USP, JP), working/secondary standards with a minimum quantity of 500mg; or,
    c. Based on the test method/specific monograph, all reference standards (related substance, internal standards, reference chemicals used for system suitability solution, resolution solution, etc.) that are used for the tests must be submitted.

3. Documents that should be included are:
    a. Method of analysis(test method); and,
    b. Certificates of analysis (COA) for FPP, primary, and working standard.

APPENDICES

Appendix 1: Product Quality Review Requirement for Well-established Multi-source Products

For an established multisource product, a product quality review may satisfy the requirements of Sections 3.2.P.2.2.1 (a), 3.2.P.2.3, (a) and 3.2.P.3.5 of the PD and DOS-PD.

A product quality review should be submitted with the objective of verifying the consistency of the quality of the FPP and its manufacturing process.

Rejected batches should not be included in the analysis but must be reported separately together with the reports of failure investigations, as indicated below.

Reviews should be conducted with not less than 10 consecutive batches manufactured over the period of the last 12 months or, where 10 batches were not manufactured in the last 12 months, not less than 10 consecutive batches manufactured over the period of the last 36 months. However, If the number of batches manufactured less than 10 over the last 36 months, the applicant needs to submit results of all batches manufactured with justification and the authority will review on a case-by-case basis.

and should include at least:

1. Review of starting and primary packaging materials used in the FPP, especially those from new sources;
2. Tabulated review and statistical analysis of quality control and in-process control results;
3. Review of all batches that failed to meet established specification(s);
4. Review of all critical deviations or non-conformances and related investigations;
5. Review of all changes carried out to the processes or analytical methods;
6. Review of the results of the stability-monitoring program;
7. Review of all quality-related returns, complaints and recalls, including export- only medicinal products;
8. Review of the adequacy of previous corrective actions;
9. List of validated analytical and manufacturing procedures and their re-validation dates;
10. Summary of sterilization validation for components and assembly, where applicable;
11. Summary of recent media-fill validation exercises;
12. Conclusion of the Annual Product Review;
13. Commitment letter that prospective validation will be conducted in the future; and,
14. The Protocol.

Notes

- Reviews must include data from all batches manufactured during the review period.
- Data should be presented in tabular or graphical form (i.e., charts or graphs), where applicable.

Appendix 2: Requirements for Registration of Products Accepted by a SRA

General Principle

This section of the guideline set the requirements for registration medicines which have been registered by the Stringent Regulatory Authority (SRA). Therefore, applicant who has submitted its application and registered its product with SRA as considered as by the Authority can follow the requirements as indicated below in this Appendix.
The authorities recognized as SRA by Food and Drug Authority include: Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Ireland, Italy, Japan, Netherlands, Norway, Switzerland, United Kingdom, United States of America, European Medicine Agency (EMA) and WHO Prequalification. However, this list of regulatory authorities will be revised periodically and as deemed necessary.

The Ethiopian Food and Drug Authority ***recognizes*** *the scientific evaluation of finished pharmaceutical products (FPPs) by these SRAs, when information about such a product submitted with the confirmatory evidence for the acceptance or registration of the product by the recognized SRA***.**

Notice: the applicant with the WHO prequalified product should follow the EFMHACA-WHO collaborative registration procedure.

The rationale behind the introduction of these procedures is that:

1. Most of the requirements and principles stipulated in this Guideline are derived from the guidance developed by ICH regions and associated countries, and from WHO Guidelines;
2. Whenever necessary, full assessment of the dossiers of the innovators can be done at any time; and,
3. The clinical studies, as well as the acceptance of the medicines for the general public health benefit, have been accepted.

Purpose

The purpose of this guidance is neither to eliminate the requirement of dossier submission nor to limit the Authority for full assessment of the product, whenever deemed to be necessary, the main purpose is to introduce a procedure that will facilitate the registration of innovator products as well as products accepted through the WHO Prequalification Program (PQP) in order to enhance the availability of the medicines to the public.

Scope

This procedure apply to both innovator and multisource (generic) finished pharmaceutical products (FPPs) approved by SRAs.

Requirements for Registration of Products Accepted by a Stringent Regulatory Authority

An applicant claiming to have a registration certificate issued by an SRA, as defined above, should submit

1. A covering letter, which should include:
    - a statement indicating that the information submitted is true and correct
    - a statement confirming that, the FPP – including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, product information – will, at the time of submission and after registration, in all respects be the same as the product registered with the reference SRA or prequalified by WHO; However
        - If composition/formulation, strength, manufacturing, specifications, are different from the product for which the MA was issued, arguments and/or data to support the applicability of the Certificate(s), and demonstration of pharmaceutical equivalence and bioequivalence should be provided in the relevant section of the dossier;
        - If the primary packaging material of the product is different from that approved by the SRA or WHO PQP, then all stability testing data generated in the new container closure system should be provided in ***the relevant section of the dossier;***
    - a statement indicating that the product is actually on the market of the reference SRA's country or region.
2. A copy of the marketing authorization, or the equivalent thereof, issued by the reference SRA to demonstrate that the product is registered or licensed in accordance with the reference SRA requirements. If applicable, a copy of the latest renewal of the marketing authorization should also be provided.
3. Public assessment report(s) and/or final acceptance letter issued by the SRA such as the Scientific Discussion of the European Public Assessment Report (EPAR), issued by the reference SRA. Assessment report(s) issued by the reference SRA that are not publicly available may be requested.
4. In the case of a WHO Prequalified product, the final acceptance letter, a copy of the WHO Public Assessment Report (WHOPAR) and copy of the consent submitted to WHO; A list of the manufacturers involved in the manufacture of the intermediate, primary packaging sites and release-testing sites, with the physical address of the

manufacturing site(s) (and unit if applicable) and approval status of the referenced SRA.

5. A list of the SRA-approved manufacturer(s) of the active pharmaceutical ingredient(s) (API(s)) used in the manufacture of the FPP, with the physical address of the manufacturing site(s) (and unit if applicable).
6. Written commitment letter to notify the Authority that whenever a pending variation, notice of concern, withdrawal, or recall is initiated, the same shall be communicated to the Authority; and,
7. The latest SRA-approved product information (summary of product characteristics (SmPC), or an equivalent thereof, the patient information leaflet (PIL), or equivalent thereof, and the labelling).

    Note: Applicant should also provide a web link to the SRA-approved product information, preferably on the website of the SRA itself, if available

8. A copy of the currently approved FPP specifications (release and shelf-life), dated and signed or certified by authorized personnel, with the analytical test procedures in appropriate section of the dossier.
9. Evidence of current and continuous manufacturing experience and a copy of the recent Annual Product quality review Report as described in Appendix 1 of medicine registration Guideline of the Authority.

    - A tabular listing of the batches manufactured for the market of the reference SRA's country since approval or during the past five years, whichever is shorter. The table should include at least the batch number, batch size (number of units), date of manufacture and packs type/size. Also provide a copy of the most recent product quality review, prepared according to the requirements of the reference SRA.

10. Complete dossiers in Module 1 through Module 5.

Appendix 3: General Recommendation for Conducting and Assessing a Dissolution Profile

The dissolution measurements of the two FPPs (e.g., test and reference (comparator), or two different strengths) should be made under the same test conditions. A minimum of three time points (zero excluded) should be included, the time points for both reference (comparator) and test product being the same. The sampling intervals should be short for a scientifically sound comparison of the profiles (e.g., 5, 10, 15, 20, 30, 45, 60, 90, 120 minutes). Inclusion of the 15-minute time point in the schedule is of strategic importance for profile similarity determinations (very rapidly dissolving scenario). For extended-release FPPs, the time points should be set to cover the entire time period of expected release, e.g., 1, 2, 3, 5, and 8 hours for a 12-hour release, and additional test intervals for a longer duration of release.

Studies should be performed in at least three (3) media covering the physiological range, including pH 1.2 hydrochloric acid, pH 4.5 buffer, and pH 6.8 buffer. Pharmacopoeia buffers are recommended; alternative buffers with the same pH and buffer capacity are also accepted. Water may be considered as an additional medium, especially when the API is unstable in the buffered media to the extent that the data is unusable.

If both the test and reference (comparator) products show more than 85% dissolution in 15 minutes, the profiles are considered similar (no calculations required).Otherwise:

- *similarity* of the resulting comparative dissolution profiles should be calculated using the following equation that defines a similarity factor (f_2)—

  $$f_2 = 50 \text{ LOG } \{[1+1/n \sum^{n}_{t=1} (R_t-T_t)^2]^{-0.5} \text{ x } 100\}$$

  where R_t and T_t are the mean percent API dissolved in reference (comparator) and test product, respectively, at each time point. An f_2 value between 50 and 100 suggests the two dissolution profiles are similar;
- a maximum of one time-point should be considered after 85% dissolution of the reference (comparator) product has been reached. In the case where 85% dissolution cannot be reached due to poor solubility of the API, the dissolution should be conducted until an asymptote (plateau) has been reached;
- at least 12 units should be used for each profile determination. Mean dissolution values can be used to estimate the similarity factor, f_2. To use mean data, the % coefficient of variation at the first time-point should be not more than 20% and at other time-points should be not more than 10%;
- when delayed-release products (e.g., enteric-coated) are being compared, the recommended conditions are acid medium (pH 1.2) for 2 hours and buffer medium (pH 6.8);
- when comparing extended-release beaded capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the API, one condition (normally the release condition) will suffice; and,
- surfactants should be avoided in comparative dissolution testing. A statement that the API is not soluble in any of the media is not sufficient and profiles, in absence of surfactants, should be provided. The rationale for the choice and concentration of surfactant should be provided. The concentration of the surfactant should be such that the discriminatory power of the test will not be compromised.

Appendix 4: Requirements for Re-registration

Any technical documents shall not be requested upon re-registration but all necessary administrative documents such as cGMP compliance status shall be submitted.

If variation is identified by the assessor during the re-registration application the Authority may impose administrative measures as per Medicine Registration Directive and other relevant law of the Country.

If applicant declare during the re-registration application, the re-registration process variation will be treated by the variation guideline of the Authority variation, the applicant needs to apply renewal application first and variation application will be followed up on approval of renewal application.

A product registration certificate is valid for five years. Therefore, an applicant is required to apply for re-registration within 180 days prior to the due date. The application for re-registration should include: Regulatory processing time date minimum of 30 working days will required.

1. Information and dossiers indicated in Module 1 of this Guideline.
    i. Cover letter,
    ii. application form (online),
    iii. Copy of valid GMP certificate or GMP waiver letter issued by the Authority
    iv. Declaration letter indicating there is no variation.

2. Tabular summary of any variations notified, accepted, and pending with the Authority since the grant of marketing authorization, if any.

Appendix 5: Product Dossier (DOS-PD) Template

The Dossier Overall Summary (DOS) is a summary that follows the scope and the outline of the body of data provided in Module 3, Module 4, and Module 5. The DOS should not include information, data, or justifications that were not already included in Module 3, Module 4, and Module 5, or in other parts of the dossier. The DOS should be completed and submitted as an electronic Word format. Where some of the sections are not applicable, an "NA" should be added, without removing its content and table format.

Section I. Quality Summary

(a) Dossier summary information:

Non-proprietary name of the finished pharmaceutical product (FPP)			
Proprietary name of the finished pharmaceutical product (FPP)			
International non-proprietary name(s) of the active pharmaceutical ingredient(s) (API(s)), including form (salt, hydrate, polymorph)			
Applicant's name and address			
Local agent/representative's name and address			
Date of submission			
Dosage form			
Reference number(s)			
Strength(s)			
Routes of administration			
Proposed indication(s)			
Contact information for the applicant's company	Name: Phone: Fax: Email:		

(b) Other information:

i. Comparator product used for in vivo bioequivalence:

Comparator product	Registered (Y/N)	Comparator product detail (strength, dosage form)	Comparator product manufacturer

ii. If the product is accepted for biowaiver, details of the biowaiver condition:

Biowaiver (Y/N)	Biowaiver condition (NA, BCS, BW, based on higher strength BE, etc.)	
	e.g., Not applicable	Solution for injection in aqueous solution

iii. Product information used for biowaiver:

Product name	Registered (Y/N)	Product used for Biowaiver (strength, dosage form)	Biowaiver accepted (Y/N)

iv. Any similar product registered and/or applied for registration:
Related dossiers (e.g., FPP(s) with the same API(s) submitted to the Authority by the applicant)

Registration/ application number	Registered (Y/N)	API, strength, dosage form	API manufacturer (including address)

v. Identify available literature references for the API and FPP:

Publication(s)	Most recent edition/ volume in which API appears/consulted	Most recent edition/ volume in which FPP appears/consulted
API status in pharmacopoeia and forum:		
Ph.Int.		
Ph.Int. monograph development (through www.who.int)*		
USP		
Pharmacopeial Forum		
Ph.Eur.		
Pharmeuropa		
BP		
Other (e.g., JP)		

*For example, monograph under development or draft/final published

SUMMARY OF LABELING AND SAMPLES ASSESSMENT **(For Authority Use Only)**
Discussion/comments on the product components of:
Summary of product characteristics: <insert assessment observations, comments, etc.>
Labeling (outer and inner labels): <insertassessment observations, comments, etc.>
Package leaflet (patient information leaflet): <insertassessment observations, comments, etc.>
Samples (e.g., FPP, device): <insertassessment observations, comments, etc.>

2.3.S DRUG SUBSTANCE or ACTIVE PHARMACEUTICAL INGREDIENT (API) (NAME, MANUFACTURER)

Complete the following table for the option that applies for the submission of API information:

Name of API:	
Name of API manufacturer:	
□	Certificate of suitability to the European Pharmacopoeia (CEP): Is a written commitment provided that the applicant will inform the Authority in the event that the CEP is withdrawn, and has acknowledged that withdrawal of the CEP will require additional consideration of the API data requirements to support the dossier: □ yes □ no (Check one) • A copy of the most current CEP (with annexes) and written commitment should be provided in Module 1; • The declaration of access should be completed by the CEP holder on behalf of the FPP manufacturer or applicant to the WHO Prequalification Programme (PQP) who refers to the CEP; and, • Summaries of the relevant information should be provided under the appropriate sections (e.g., S.1.3, S.3.1, S.4.1 –S.4.4, S.6 and S.7; see Quality Guideline (module 3)).
□	For WHO PQP-accepted API: • APIMF number assigned by WHO (if known): _____ ; version number (and/or date) of the Open part: _____ ; version number (and/or date) of the Closed part: _____ ; • A copy of the letter of access should be provided in Module 1; and, • Summaries of the relevant information from the Open part should be provided under the appropriate sections. See Section 3.2.S in this Guideline.
□	Full details in the Product Dossier: Summaries of the full information should be provided under the appropriate sections of Module 2, and full details of the DMF and/or APIMF (Open or restricted part) should be provided in Module 3.

2.3.S.1 General Information (name, manufacturer)

2.3.S.1.1 Nomenclature (name, manufacturer)

(a) International Non-proprietary name (INN)[Recommended]:
(b) Compendial name, if relevant:
(c) Chemical name(s):
(d) Company or laboratory code:
(e) Other nonproprietary name(s) (e.g., national name, USAN, BAN):
(f) Chemical Abstracts Service (CAS) registry number:

2.3.S.1.2 Structure (name, manufacturer)

(a) Structural formula, including relative and absolute stereochemistry:
(b) Molecular formula:
(c) Relative molecular mass:

2.3.S.1.3 General Properties (name, manufacturer)

(a) Physical description (e.g., appearance, color, physical state):
(b) Solubility:
– In common solvents:
– Quantitative aqueous pH solubility profile (pH 1.2 to 6.8):

	Medium (e.g., buffer)	Solubility (mg/ml)
1.2		
4.5		
6.8		

Dose/solubility volume calculation:

(c) Physical form (e.g., polymorphic form(s), solvate, hydrate):
– Polymorphic form:
– Solvate:
– Hydrate:
(d) Other:

Property	
pH	
pK	
Partition coefficients	
Melting/boiling points	
Specific optical rotation (specify solvent)	
Refractive index (liquids)	
Hygroscopicity	
UV absorption maxima/molar absorptivity	
Other	

2.3.S.2 Manufacture (Name, Manufacturer)

2.3.S.2.1 Manufacturer(s) (Name, Manufacturer)

(a) Name, address and responsibility (e.g., production, packaging, labeling, testing, storage) of each manufacturer, including contractors, and each proposed manufacturing site or facility involved:

Name and address (including block(s)/unit(s))	Responsibility	APIMF/CEP number (if applicable)

(b) Manufacturing authorization for the production of API(s) and certificate of GMP compliance (copy of GMP certificate should be provided in Module 1):

2.3.S.2.2 Description of Manufacturing Process and Process Controls (Name, Manufacturer)

(a) Flow diagram of the synthesis process(es):
(b) Brief narrative description of the manufacturing process(es):
(c) Alternate manufacturing process(es) and explanation:
(d) Reprocessing steps and justification:

2.3.S.2.3 Control of Materials (Name, Manufacturer)

(a) Summary of the quality and controls of the starting materials used in the manufacture of the API:

Step/Starting material	Test(s)/Method(s)	Acceptance criteria

(b) Name and manufacturing site address of starting material manufacturer(s):
(c) Where the API(s) and the starting materials and reagents used to manufacture the API(s) are without risk of transmitting agents of animal spongiform encephalopathies, a letter of attestation confirming this can be found in:

2.3.S.2.4 Controls of Critical Steps and Intermediates (Name, Manufacturer)

(a) Summary of the controls performed at critical steps of the manufacturing process and on intermediates:

Step/Materials	Test(s)/Method(s)	Acceptance criteria

2.3.S.2.5 Process Validation and/or Evaluation (Name, Manufacturer)

(a) Description of process validation and/or evaluation studies (e.g., for aseptic processing and sterilization):

2.3.S.2.6 Manufacturing Process Development (Name, Manufacturer)

(b) Description and discussion of the significant changes made to the manufacturing process and/or manufacturing site of the API used in producing comparative bioavailability or biowaiver, stability, scale-up, pilot- and, if available, production-scale batches:

2.3.S.3 Characterization (Name, Manufacturer)

2.3.S.3.1 Elucidation of Structure and other Characteristics (Name, Manufacturer)

(a) List of studies performed (e.g., IR, UV, NMR, MS, elemental analysis) and conclusion from the studies (e.g., whether results support the proposed structure):

(b) Discussion on the potential for isomerism and identification of stereochemistry (e.g., geometric isomerism, number of chiral centers and configurations) of the API batch(es) used in comparative bioavailability or biowaiver studies:

(c) Summary of studies performed to identify potential polymorphic forms (including solvates):

(d) Summary of studies performed to identify the particle size distribution of the API:

(e) Other characteristics:

2.3.S.3.2 Impurities (Name, Manufacturer)

(a) Identification of potential and actual impurities arising from the synthesis, manufacture, and/or degradation:

i. List of API-related impurities (e.g., starting materials, by-products, intermediates, chiral impurities, degradation products), including chemical name, structure, and origin:

API-related impurity (chemical name or description)	Structure	Origin

ii. List of process-related impurities (e.g., residual solvents, reagents), including compound names and step(s) used in synthesis:

Process-related impurity (compound name)	Step used in synthesis

(b) Basis for setting the acceptance criteria for impurities:

i. Maximum daily dose (i.e., the amount of API administered per day) for the API, corresponding to ICH Reporting/Identification/Qualification Thresholds for the API-related Impurities and the concentration limits (ppm) for the process-related impurities (e.g., residual solvents):

Maximum daily dose for the API:	<x mg/day>	
Test	Parameter	ICH threshold or concentration limit
API-related impurities	Reporting Threshold	
	Identification Threshold	
	Qualification Threshold	
Process-related impurities	<solvent 1>	
	<solvent 2>, etc.	

ii. Data on observed impurities for relevant batches (e.g., comparative bioavailability or biowaiver, stability batches):

Impurity (API-related and process-related)	Acceptance Criteria	Results (include batch number* and use**)		

* Include strength, if reporting impurity levels found in the FPP (e.g., for comparative studies)

** E.g., comparative bioavailability or biowaiver studies, stability

iii. Justification of proposed acceptance criteria for impurities:

2.3.S.4 Control of the API (Name, Manufacturer)

2.3.S.4.1 Specification (Name, Manufacturer)

(a) API specifications of the FPP manufacturer:

Standard (e.g., Ph.Int., Ph.Eur., BP, USP, House)		
Specification reference number and version		
Test	Acceptance criteria	Analytical procedure (type/source/version)
Description		
Identification		
Impurities		
Assay		
Other		

2.3.S.4.2 Analytical Procedures (Name, Manufacturer)

(a) Summary of the analytical procedures (e.g., key method parameters, conditions, system suitability testing):

See 2.3.R REGIONAL INFORMATION for summaries of the analytical procedures and validation information (i.e., 2.3.R.2 Analytical Procedures and Validation Information).

2.3.S.4.3 Validation of Analytical Procedures (Name, Manufacturer)

(a) Summary of the validation information (e.g., validation parameters and results):

See 2.3.R REGIONAL INFORMATION for summaries of the analytical procedures and validation information (i.e., 2.3.R.2 Analytical Procedures and Validation Information).

2.3.S.4.4 Batch Analyses of the API from the FPP Manufacturer for Relevant Batches (e.g., comparative bioavailability or biowaiver, stability):

(a) Description of the batches:

Batch number	Batch size	Date and site of production	Use (e.g., comparative bioavailability or biowaiver, stability)

(b) Summary of batch analyses test results of the FPP manufacturer:

Test	Acceptance Criteria	Results		
		<batch x>	<batch y>	<batch z>
Description				
Identification				
Impurities				
Assay				
Other				

(c) Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.S.4.2 and 2.3.S.4.3 (e.g., historical analytical procedures):

2.3.S.4.5 Justification of Specification (Name, Manufacturer)

(a) Justification of the API specification (e.g., evolution of tests, analytical procedures and acceptance criteria, differences from officially recognized compendial standard(s)):

2.3.S.5 Reference Standards or Materials (Name, Manufacturer)

(a) Source (including lot number) of primary reference standards or reference materials (e.g., Ph.Int., Ph.Eur., BP, USP, House):

(b) Characterization and evaluation of unofficial (e.g., not from an officially recognized pharmacopoeia) primary reference standards or reference materials (e.g., elucidation of structure, certificate of analysis):

(c) Description of the process controls of the secondary reference standard (comparative certificate of analysis and IR spectra against primary standard):

2.3.S.6 Container Closure System (Name, Manufacturer)

(a) Description of the container closure system(s) for the shipment and storage of the API (including the identity of materials of construction of each primary packaging component and a brief summary of the specifications):

Packaging component	Materials of construction	Specifications (list parameters e.g., identification (IR))

(b) Other information on the container closure system(s) (e.g., suitability studies):

2.3.S.7 Stability (Name, Manufacturer)

2.3.S.7.1 Stability Summary and Conclusions (Name, Manufacturer)

(a) Summary of stress testing (e.g., heat, humidity, oxidation, photolysis, acid/base) and results:

Stress condition	Treatment	Results (e.g., including discussion whether mass balance is observed)
Heat		
Humidity		
Oxidation		
Photolysis		
Acid		
Base		
Other		

(b) Summary of accelerated and long-term testing parameters (e.g., studies conducted):

Storage condition (°C, % RH)	Batch number	Batch size	Container closure system	Completed (and proposed) testing intervals

(c) Summary of the stability results observed for the above accelerated and long-term studies:

Test	Results
Description	
Moisture	
Impurities	
Assay	
Other	

(d) Proposed storage statement and re-test period (or shelf-life, as appropriate):

Container closure system	Storage statement	Re-test period*

* Indicate if a shelf-life is proposed in lieu of a re-test period (e.g., in the case of labile APIs)

2.3.S.7.2 Post-approval Stability Protocol and Stability Commitment (Name, Manufacturer)

(a) Stability protocol for PRIMARY stability batches (e.g., storage conditions (including tolerances), batch numbers and batch sizes, tests and acceptance criteria, testing frequency, and container closure system(s)):

Parameter	Details	
Storage condition(s) (°C, % RH)		
Batch number(s)/batch size(s)		
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	Other	
Testing frequency		
Container closure system(s)		

(b) Stability protocol for COMMITMENT batches (e.g., storage conditions (including tolerances), batch numbers (if known) and batch sizes, tests and acceptance criteria, testing frequency, and container closure system(s)):

Parameter	Details	
Storage condition(s) (°C, % RH)		
Batch number(s)/batch size(s)	<not less than three production batches>	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	

Parameter	Details	
	Other	
Testing frequency		
Container closure system(s)		

(c) Stability protocol for ONGOING batches (e.g., storage conditions (including tolerances), batch sizes and annual allocation, tests and acceptance criteria, testing frequency, and container closure system(s)):

Parameter	Details	
Storage condition(s) (◦C, % RH)		
Annual allocation	<at least one production batch per year (unless none is produced that year) in each container closure system >	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	Other	
Testing frequency		
Container closure system(s)		

2.3.S.7.3 Stability Data (Name, Manufacturer)

(a) The actual stability results should be provided in Module 3.

(b) Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.S.4 (e.g., analytical procedures used only for stability studies):

2.3.P DRUG PRODUCT or FINISHED PHARMACEUTICAL PRODUCT (FPP)

2.3.P.1 Description and Composition of the FPP

(a) Description of the FPP:

(b) Composition of the FPP:

i. Composition, i.e., list of all components of the FPP and their amounts on a per unit basis and percentage basis (including individual components of mixtures prepared in-house (e.g., coatings) and overages, if any):

Component and quality standard (and grade, if applicable)	Function	Strength (label claim)					
		Quantity per unit	%	Quantity per unit	%	Quantity per unit	%
<complete with appropriate title, e.g., Core tablet, Contents of capsule, Powder for injection>							
Subtotal 1							
<complete with appropriate title, e.g., Film-coating >							

Component and quality standard (and grade, if applicable)	Function	Strength (label claim)					
		Quantity per unit	%	Quantity per unit	%	Quantity per unit	%
Subtotal 2							
Total							

ii. Composition of all components purchased as mixtures (e.g., colorants, coatings, capsule shells, imprinting inks):

(c) Description of accompanying reconstitution diluent(s), if applicable:

(d) Type of container closure system used for the FPP and accompanying reconstitution diluent, if applicable:

2.3.P.2 Pharmaceutical Development

2.3.P.2.1 Components of the FPP

2.3.P.2.1.1 Active Pharmaceutical Ingredient

(a) Discussion of the:

i. compatibility of the API(s) with excipients listed in 2.3.P.1:

ii. key physicochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic or solid state form) of the API(s) that can influence the performance of the FPP:

iii. for fixed-dose combinations, compatibility of APIs with each other:

2.3.P.2.1.2 Excipients

(a) Discussion of the choice of excipients listed in 2.3.P.1 (e.g., their concentrations, their characteristics that can influence the FPP performance):

2.3.P.2.2 Finished Pharmaceutical Product

2.3.P.2.2.1 Formulation Development

(a) Summary describing the development of the FPP (e.g., route of administration, usage, optimization of the formulation, etc.):

(b) Information on primary (submission, registration, exhibit) batches, including comparative bioavailability or biowaiver, stability, commercial:

i. Summary of batch numbers:

Batch number(s) of the FPPs used in:			
Bioequivalence or biowaiver			
Dissolution profile studies			
Stability studies (primary batches)			
‹packaging configuration I›			
‹packaging configuration II›			
‹Add/delete as many rows as necessary›			
Stability studies (production batches)			
‹packaging configuration I›			
‹packaging configuration II›			

(Add/delete as many rows as necessary)			
Validation studies (primary batches) if available			
‹packaging configuration I›			
‹packaging configuration II›			
(Add/delete as many rows as necessary)			
Validation studies (at least the first three consecutive production batches) or code(s)/version(s) for process validation protocol(s)			

ii. Summary of formulations and discussion of any differences:

Component and quality standard (e.g., NF, BP, Ph.Eur, House)	Relevant Batches							
	Comparative bioavailability or biowaiver		Stability		Process validation		Commercial (2.3.P.1)	
	<Batch nos. and sizes>		<Batch nos. and sizes>		<Batch nos. and sizes>		<Batch nos. and sizes>	
	Theor. quantity per batch	%	Theor. quantity per batch	%	Theor. quantity per batch	%	Theor. quantity per batch	%
<complete with appropriate title e.g., Core tablet, Contents of capsule, Powder for injection>								
Subtotal 1								
<complete with appropriate title, e.g., Film-coating >								
Subtotal 2								
Total								

(c) Description of batches used in the comparative in vitro studies (e.g., dissolution) and in the in vivo studies (e.g., comparative bioavailability or biowaiver), including strength, batch number, type of study, and reference to the data (volume, page):

(d) Summary of results for comparative in vitro studies (e.g., dissolution):

(e) Summary of any information on in vitro–in vivo correlation (IV-IVC) studies (with cross-reference to the studies in Module 5):

(f) For scored tablets, provide the rationale/justification for scoring:

2.3.P.2.2.2 Overages

(a) Justification of overages in the formulation(s) described in 2.3.P.1:

2.3.P.2.2.3 Physicochemical and Biological Properties

(a) Discussion of the parameters relevant to the performance of the FPP (e.g., pH, ionic strength, dissolution, particle size distribution, polymorphism, rheological properties):

2.3.P.2.3 Manufacturing Process Development

(a) Discussion of the development of the manufacturing process of the FPP (e.g., optimization of the process, selection of the method of sterilization):

(b) Discussion of the differences in the manufacturing process(es) for the batches used in the comparative bioavailability or biowaiver studies and the process described in 2.3.P.3.3:

2.3.P.2.4 Container Closure System

(a) Discussion of the suitability of the container closure system (described in 2.3.P.7) used for the storage, transportation (shipping), and use of the FPP (e.g., choice of materials, protection from moisture and light, compatibility of the materials with the FPP):

(b) For a device accompanying a multi-dose container, a summary of the study results demonstrating the reproducibility of the device (e.g., consistent delivery of the intended volume):

2.3.P.2.5 Microbiological Attributes

(a) Discussion of microbiological attributes of the FPP (e.g., preservative effectiveness studies):

2.3.P.2.6 Compatibility

(a) Discussion of the compatibility of the FPP (e.g., with reconstitution diluent(s) or dosage devices, co-administered FPPs):

2.3.P.3 Manufacture

2.3.P.3.1 Manufacturer(s)

(a) Name, address, and responsibility (e.g., manufacturing, packaging, labeling, testing) of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing:

Name and address (include block(s)/unit(s))	Responsibility

(b) Manufacturing authorization, marketing authorization, and, where available, WHO-type certificate of GMP (GMP information should be provided in Module 1):

2.3.P.3.2 Batch Formula

(a) List of all components of the FPP to be used in the manufacturing process and their amounts on a per batch basis (including individual components of mixtures prepared in-house (e.g., coatings),overages, and those that may be removed during processing (solvents, Nitrogen, silicon, etc.):

Strength (label claim)			
Master production document reference number and/or version			
Proposed commercial batch size(s) (e.g., number of dosage units)			
Component and quality standard (and grade, if applicable)	Quantity per batch (e.g., kg/batch)	Quantity per batch (e.g., kg/batch)	Quantity per batch (e.g., kg/batch)
<complete with appropriate title e.g., Core tablet, Contents of capsule, Powder for injection>			
Subtotal 1			
<complete with appropriate title e.g., Film-coating >			
Subtotal 2			
Total			

2.3.P.3.3 Description of Manufacturing Process and Process Controls

(a) Flow diagram of the manufacturing process:

(b) Narrative description of the manufacturing process, including equipment type and working capacity, process parameters:

(c) Justification of reprocessing of materials, if any:

2.3.P.3.4 Controls of Critical Steps and Intermediates

(a) Summary of controls performed at the critical steps of the manufacturing process and on isolated intermediates:

Step(e.g., granulation, compression, filling, coating)	Control parameter and frequency

2.3.P.3.5 Process Validation and/or Evaluation

(a) Summary of the process validation and/or evaluation studies conducted (including product quality review(s) where relevant), and/or a summary of the proposed process validation protocol for the critical steps or critical assays used in the manufacturing process (e.g., protocol number, parameters, results):

2.3.P.4 Control of Excipients

2.3.P.4.1 Specifications

(a) Summary of the specifications for officially recognized compendial excipients which include supplementary tests not included in the officially recognized compendial monograph(s):

2.3.P.4.2 Analytical Procedures

(a) Summary of the analytical procedures for supplementary tests not included in compendial monograph:

2.3.P.4.3 Validation of Analytical Procedures

(a) Summary of the validation information for the analytical procedures for supplementary tests (where applicable):

2.3.P.4.4 Justification of Specifications

(a) Justification of the specifications (e.g., evolution of tests, analytical procedures and acceptance criteria, exclusion of certain tests, differences from officially recognized compendial standard(s)):

2.3.P.4.5 Excipients of Human or Animal Origin

(a) For FPPs using excipients without risk of transmitting agents of animal spongiform encephalopathies, a letter of attestation confirming this (provide copy of attestation letter in Module 1):

2.3.P.4.6 Novel Excipients

Full details of manufacture, characterization, and controls as well as supporting safety and clinical data in Modules 4 and 5.

2.3.P.5 Control of FPP

2.3.P.5.1 Specification(s)

(a) Specification(s) for the FPP:

Standard (e.g., Ph.Int., BP, USP, House)			
Specification reference number and version			
Test	Acceptance criteria (release)	Acceptance criteria (shelf-life)	Analytical procedure (type/source/version)
Description			
Identification			
Impurities			
Assay			
Other			

2.3.P.5.2 Analytical Procedures

(a) Summary of the analytical procedures (e.g., key method parameters, conditions, system suitability testing):

See 2.3.R REGIONAL INFORMATION for summaries of the analytical procedures and validation information (i.e., 2.3.R.2 Analytical Procedures and Validation Information).

2.3.P.5.3 Validation of Analytical Procedures

(a) Summary of the validation information (e.g., validation parameters and results):
See 2.3.R REGIONAL INFORMATION for summaries of the analytical procedures and validation information (i.e., 2.3.R.2 Analytical Procedures and Validation Information).

2.3.P.5.4 Batch Analyses

(a) Description of the batches:

Strength and batch number	Batch size	Date and site of production	Use (e.g., comparative bioavailability or biowaiver, stability)

(b) Summary of batch analyses test results for relevant batches (e.g., comparative bioavailability or biowaiver, stability):

Test	Acceptance Criteria	Results		
		<batch x>	<batch y>	<batch z>
Description				
Identification				
Impurities				
Assay				
Other				

2.3.P.5.5 Characterization of Impurities

(a) Identification of potential and actual impurities:

Degradation product (chemical name or descriptor)	Structure	Origin

Process-related impurity (compound name)	Step used in the FPP manufacturing process

(b) Basis for setting the acceptance criteria for impurities:

i. Maximum daily dose (i.e., the amount of API administered per day) for the API, corresponding ICH Reporting/Identification/Qualification Thresholds for the

degradation products in the FPP, and the concentration limits (ppm) for the process-related impurities (e.g., residual solvents):

Maximum daily dose for the API:	<x mg/day>	
Test	Parameter	ICH threshold or concentration limit
Degradation product	Reporting Threshold	
	Identification Threshold	
	Qualification Threshold	
Process-related impurities	<solvent 1>	
	<solvent 2>, etc.	

ii. Data on observed impurities for relevant batches (e.g., comparative bioavailability or biowaiver):

Impurity (degradation product and process-related)	Acceptance Criteria	Results		
		<batch no., strength, use>	<batch no., strength, use>	<batch no., strength, use>

iii. Justification of proposed acceptance criteria for impurities:

2.3.P.5.6 Justification of Specification(s)

(a) Justification of the FPP specification(s) (e.g., evolution of tests, analytical procedures and acceptance criteria, differences from officially recognized compendial standard(s)):

2.3.P.6 Reference Standards or Materials

(a) Source (including lot number) of primary reference standards or reference materials (e.g., Ph.Int., Ph.Eur., BP, USP, House) not discussed in 3.2.S.5:

(b) Characterization and evaluation of unofficial (e.g., not from an officially recognized pharmacopoeia) primary reference standards or reference materials (e.g., elucidation of structure, certificate of analysis) not discussed in 3.2.S.5:

(c) Description of the process controls of the secondary reference standard (comparative certificate of analysis and IR spectra against primary standard) not discussed in 3.2.S.5:

2.3.P.7 Container Closure System

(a) Description of the container closure systems, including unit count or fill size, container size, or volume:

Description (including materials of construction)	Strength	Unit count or fill size	Container size

(b) Summary of specifications of each primary and functional secondary (e.g., foil pouches) packaging components:

Packaging component	Specifications (list parameters e.g., identification (IR))
HDPE bottle	
PP cap	
Induction sealed liners	
Blister films (PVC, etc.)	
Aluminum foil	
Other	

(c) Other information on the container closure system(s):

2.3.P.8 Stability

2.3.P.8.1 Stability Summary and Conclusions

(a) Summary of stress testing and results (e.g., photostability studies, cyclic studies, freeze-thaw studies):

(b) Summary of accelerated and long-term testing parameters (e.g., studies conducted):

Storage conditions (°C, % RH)	Strength and batch number	Batch size	Container closure system	Completed/proposed test intervals

(c) Summary of the stability results observed for the above accelerated and long-term studies:

Test	Results
Description	
Moisture	
Impurities	
Assay	

Test	Results
Other	

(d) Proposed storage statement and shelf-life (and in-use storage conditions and in-use period, if applicable):

Container closure system	Storage statement	Shelf-life

2.3.P.8.2 Post-approval Stability Protocol and Stability Commitment

(a) Stability protocol for Primary stability batches (e.g., storage conditions (including tolerances), batch numbers and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):

Parameter	Details	
Storage condition(s) (°C, % RH)		
Batch number(s)/batch size(s)		
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	Other	
Testing frequency		
Container closure system(s)		

(b) Stability protocol for COMMITMENT batches (e.g., storage conditions (including tolerances), batch numbers (if known) and batch sizes, tests and acceptance criteria, testing frequency, and container closure system(s)):

Parameter	Details	
Storage condition(s) (◦C, % RH)		
Batch number(s) / batch size(s)	<not less than three production batches in each container closure system>	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	Other	
Testing Frequency		
Container Closure System(s)		

(c) Stability protocol for ONGOING batches (e.g., storage conditions (including tolerances), number of batches per strength and batch sizes, tests and acceptance criteria, testing frequency, and container closure system(s)):

Parameter	Details	
Storage condition(s) (°C, % RH)		
Batch size(s), annual allocation	<at least one production batch per year (unless none is produced that year) in each container closure system >	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	Other	
Testing frequency		
Container closure system(s)		

2.3.P.8.3 Stability Data

(a) The actual stability results should be provided in Module 3.

(b) Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.P.5 (e.g., analytical procedures used only for stability studies):

(c) Bracketing and matrixing design and justification for COMMITMENT and/or ONGOING stability batches, if applicable:

2.3.A APPENDICES

2.3.A.1 Facilities and Equipment (Name, Manufacturer)

(a) Summary of information on facilities and equipment, in addition to the information provided in other sections of the submission (for sterile product manufacturing only):

2.3.A.2 Adventitious Agents Safety Evaluation (Name, Dosage Form, Manufacturer)

(a) Summary of the information assessing the risk with respect to potential contamination with adventitious agents:

2.3.A.3 Excipients

(a) Summary of the details of manufacture, characterization, and controls, with cross references to supporting safety data (nonclinical and/or clinical) for the novel excipients:

2.3.RREGIONAL INFORMATION

2.3.R.1 Production Documentation

2.3.R.1.1 Executed Production Documents

(a) List of batches (including strengths) for which executed production documents have been provided (e.g., comparative bioavailability or biowaiver batches):

2.3.R.1.2 Master Production Documents

(a) The blank master production documents for each strength, proposed commercial batch size, and manufacturing facility should be provided in Module 3.

2.3.R.2 Analytical Procedures and Validation Information

ANALYTICAL PROCEDURES AND VALIDATION INFORMATION SUMMARIES

ATTACHMENT NUMBER:	

HPLC Method Summary		Volume/Page:	
Method name:			
Method code:		Version and/or Date:	
Column(s)/temperature (if other than ambient):			
Mobile phase (specify gradient program, if applicable):			
Detector (and wavelength, if applicable):			
Flow rate:			
Injection volume:			
Sample solution concentration (expressed as mg/ml, let this be termed "A"):			
Reference solution concentration (expressed as mg/ml and as % of "A"):			
System suitability solution concentration (expressed as mg/ml and as % of "A"):			
System suitability tests (tests and acceptance criteria):			
Method of quantification (e.g., against API or impurity reference standard(s)):			
Other information (specify):			

ATTACHMENT NUMBER:	

Validation Summary		Volume/Page:			
Analytes:					
Typical retention times (RT):					
Relative retention times (RTImp./RTAPI or Int. Std.):					
Relative response factor (RFImp./RFAPI):					
Specificity:					
Linearity/Range:	Number of concentrations: Range (expressed as % "A"): Slope: Y-intercept: Correlation co-efficient (r2) :				
Accuracy:	Conc.(s) (expressed as % "A"): Number of replicates: Percent recovery (avg/RSD):				

ATTACHMENT NUMBER:		
Precision/ Repeatability: (intra-assay precision)	Conc.(s) (expressed as % “A”): Number of replicates: Result (avg/RSD):	
Precision/ Intermediate Precision: (days/analysts/equipment)	Parameter(s) altered: Result (avg/RSD):	
Limit of Detection (LOD) (expressed as % “A”):		
Limit of Quantitation (LOQ) (expressed as % “A”):		
Robustness:	Stability of solutions: Other variables/effects:	
Typical chromatograms or spectra may be found in:		
Company(ies) responsible for method validation:		
Other information (specify):		

Conclusion, Recommendation, and Questions to the applicant: **(For Authority Use Only)** (Discussions to be inserted under each section)	
General Remarks:	
API Question (write the name of the API):	
FPP Question (write the name of FPP):	
Name(s) of assessor(s):	Date:

Section II. Safety and Efficacy Summary

2.3.B SUMMARY OF BIOEQUIVALENCE STUDY

Where applicable, bioequivalence data for demonstration of safety and efficacy inter-changeability as described in Annex IV of this Guideline should be provided in Module 5 of the dossier. Where the equivalence is demonstrated on the basis of biowaiver, completion of the relevant section of 2.3.B of the DOS, together with discussion of the dissolution profile study under 2.3.P.2.2.1.d and dissolution profile data in Module 3 of the dossier, should be provided.

2.3.B.1 Description and Composition of the Product

(a) Description of the bio-batch/biowaiver batch and justification for any difference the composition described under 2.3.P.1:

(b) Composition of the bio-batch/biowaiver batch, if different from, and justification for any difference with the composition described under 2.3.P.1:

Component and Quality Standard	Function	Strength (label claim)			
		XX mg		XX mg	
		Quantity per unit	%*	Quantity per unit	%*
TOTAL					

*Each ingredient expressed as a percentage of the total core or coating weight

Composition of the batches used for clinical, bioequivalence or dissolution profile studies				
Batch number:				
Batch size (number of unit doses)*:				
Comments, if any:				
Comparison of unit dose compositions and of clinical FPP batches: (Duplicate this table for each strength, if compositions are different)				
Ingredients	Unit dose (mg)	Unit dose (%)	Bio-batch (kg)	Bio-batch (%)
Equivalence of the compositions or justified differences				

*Bioequivalence batches should be at least of pilot-scale (10% of production- scale or 100,000 capsules/tablets, whichever is greater) and manufacturing method should be the same as for production-scale.

2.3.B.2 Clinical Study Report Summary

(a) Study protocol
   i. Study #:
   ii. Study title:
   iii. Location of study protocol:
   iv. Start and stop dates for each phase of the clinical study:

(b) Study ethics
   i. Name of review committee, date of approval of protocol and consent form, location of approval letter in the submission dossier:
   ii. Location of a reference copy of the informed consent form:

(c) Investigator and study administration
   i. Name of principal investigator:
   ii. Clinical facility:
   iii. Clinical laboratories:
   iv. Analytical laboratories:
   v. Company performing pharmacokinetic/statistical analysis:

(d) Study objective

2.3.B.3 Investigational Plan

(a) Overall study design and plan description:
(b) Selection of study population:
(c) Inclusion criteria:
(d) Exclusion criteria:
(e) Removal of trial subject from trial or assessment:
(f) Number of subjects enrolled in the study:
(g) Withdrawals:
(h) Health verification test criteria, study site normal value and date test performed, and results outside study site normal value:

2.3.B.4 Study Product Administered

(a) Summary of study product information:

Product	Batch number	Batch size	Manufacturing Date	Potency(measured content) as % of label claim*
Test Product				
Reference Product				

* This information should be cross-referenced to the location of the certificate of analysis and validated analytical method in the submission dossier.

(b) Purchase, shipment, storage of the reference product:
(This information should be cross-referenced to location in submission of documents (e.g., receipts).)

(c) Justification of choice of reference product:
(Provide short summary here and cross-reference to location of comprehensive justification in the submission dossier.)

2.3.B.5 Study Dose Administration

(a) Dose administered(indicate number of dosage units comprising a single dose, e.g., 200 mg as 1 x 200 mg or 2 x 100 mg tablets):
(b) Volume and type of fluid consumed with the dose:
(c) Interval between doses (washout period):
(d) Food and fluid administration:
(e) Restrictions on physical activity and routine practice during study:

2.3.B.6 Study Blinding

(a) Identify which of the following were blinded.(If any of the groups were not blinded, provide a justification for not doing so.)

Groups	Blinding (Y/N)	Reason for not blinding
Study monitors		
Subjects		
Analysis		

(b) Provide the responsibility for holding the blinding code and the condition for breaking the code:

2.3.B.7 Sampling for Drug Concentration Measurement

(a) Biological fluids sampled:
(b) Sampling protocol:
(c) Number of samples collected per subject:
(d) Volume of fluid collected per sample:
(e) Total volume of samples collected per subject per phase of the study:
(f) Sampling time:
(g) Deviation from the sampling protocol:
(h) Sample collection procedure:
(i) Storage procedure and condition:

2.3.B.8 Trial Subject

(a) Demographic characteristics:
(b) Study population (i.e., normal, healthy adult volunteers or patients):
(c) Summary of ethnic group and gender:
(d) Subjects noted to have special characteristics (e.g., fast acetylators):
(e) Range and mean age ±SD of study subjects:
(f) Subjects whose ratio is not within ±15% of the values given on a standard height/weight table:
(g) Number of smokers included in the study (indicate justification on the impact of the study and number of cigarettes per day):

2.3. B.9 Safety Evaluation

2.3.B.9.1 Adverse event observed

(List any adverse events by subject number. State whether a reaction occurred following administration of the test or reference product, identify any causal relationships, and note any treatments required. State the location of this summary in the submission.)

(Discuss the implications of the observed adverse events with respect to bioequivalence)

2.3.B.10 Efficacy Evaluation

(a) Location of mean and individual subject drug concentration in the submission dossier:

(b) Location of mean and individual subject linear and semi-logarithmic drug concentration:

(c) Pharmacokinetic parameters:

Parameter	Test			Reference		
	Arithmetic Mean	Standard deviation	Inter-individual coefficient of variation (%)	Arithmetic Mean	Standard deviation	Inter-individual coefficient of variation (%)
AUCT (units)*						
AUC∞ (units)						
Cmax (units)						
Tmax (units)						
T½(units)						
Ratio of AUCT/AUC∞						

(Locate in the submission dossier method for the calculation of AUC and extrapolation)

(a) Statistical Analysis

i. Provide the following results from the ANOVA (parametric) on the logarithmically transformed AUCT and C_{MAX} and other relevant parameters, e.g., in the case of steady-state designs, AUCτ , C_{MAX} , and C_{MIN}; state the software used for computing ANOVA.

ii. Geometric means, results from ANOVA, degrees of freedom (DF), and derived CV (intra-individual):

Parameter	Test	Reference	% Ratio of geometric means	90 % confidence interval	DF	CV (%)
AUCT (units)						
AUCI (units)						
Cmax (units)						

iii. Period and/or sequence effects:
State whether any period and/or sequence effects have been found. If yes, provide a brief discussion of those effects here, and state the location in the submission dossier where a comprehensive explanation is provided.

2.3.B.11 Discussion of Results

Indicate the location of the discussion of results in the submission dossier. If the discussion currently included in the study report does not include comparisons of results of this study, including inter- and intra-individual variability, with published results (literature, product information of reference product (innovator)), such a discussion should be provided here and copies of the references used should be provided in Module 5 of the submission dossier.

2.3.B.12 Bio-Analytical Study Report

(a) Analytical techniques used:
(b) Analytical protocol number (indicate location in the submission dossier):
(c) Type of analyte(s) monitored:
(d) Method of detection:
(e) Reference standard used:
(f) Internal standard used (citation for reference):
(g) Date of subject sample analysis:
(h) Longest period subject sample storage (Indicate the time elapsed between the first day of sample collection and the last day of subject sample analysis. Indicate whether all samples for a given subject were analyzed together in a single analysis run.):
(i) Standard curves (Locate in the submission dossier the tabulated raw data and back-calculated data with descriptive statistics.):
(j) List of curves run during the study and concentration of calibration standards used:
(k) Summary of descriptive data, including slope, intercept, and correlation coefficients:
(l) Regression model used, including any weighing:
(m) Limit of quantitation (LOQ) (Summarize inter-day and intra-day precision and accuracy at the LOQ.)
(n) Quality control samples:
    i. Identify the concentrations of the QC samples, their dates of preparation, and the storage conditions employed prior to their analysis:
    ii. State the number of QC samples in each analytical run per concentration:
(o) Precision and accuracy:
    Summarize inter-day and intra-day precision and accuracy of QC samples analyzed during subject sample analysis and inter-day precision of back-calculated standards.
(p) Repeat analysis:
    i. List repeats by sample identification, and include the following information for each repeat :initial value; reason for repeat; repeat value(s); accepted value; and reason for acceptance:
    ii. Report the number of repeats as a percentage of the total number samples assayed.
(q) Chromatograms:

State the location in the submission dossiers where the sample chromatograms can be found. The chromatograms should be obtained from a minimum of two analytical batches and include at least 20% of the subjects, up to a maximum of five.

A complete set includes standards, QC samples, and pre-dose and post-dose subject samples for both phases. Each chromatogram should be clearly labeled with respect to the following: date of analysis; subject ID number; study period; sampling time; analyte; standard or QC, with concentration; analyte and internal standard peaks; and peak heights and/or areas.

2.3.B.13 Bioanalytical Validation Report

(a) Precision and accuracy:
(b) Summary of inter-day and intra-day accuracy and precision during assay validation:
(c) Stability (Provide location of the raw data, a description of the methodology employed, and a summary of the data.):
(d) Summary of data on long term storage condition:
    i. Summary of data on freeze–thaw stability:
    ii. Summary data on bench-top stability:
    iii. Summary data on auto sampler storage stability:
(e) Specificity(methods to verify specificity against endogenous/exogenous compounds and results):
(f) Matrix effect (in case of MS detection; methods to verify the matrix effect and results):
(g) Recovery (method and results of assessment for analyte and internal standard, including mean and CV%):

2.3.B.14 Study Quality Assurance

(a) Internal quality assurance method:
State locations in the submission dossier where internal quality assurance methods and results are described for each of the study sites.
(b) Monitoring, auditing, and inspection:
Provide a list of all monitoring and auditing reports of the study, and of recent inspections of study sites by regulatory agencies. State the locations in the submission of the respective reports for each of study sites.

Conclusion, Recommendations, and Questions to the Applicant (For Authority Use Only) (Discussions to be inserted under each section)	
General Remarks:	
API Question (write the name of the API):	
FPP Question (write the name of FPP):	
Name(s) of assessor(s):	Date:

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